VOL. 34 APRIL 1958 NO. 4

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

C. SIDNEY BURWELL

WILLIAM J. EISENMENGER

C. STUART WELCH, EDWARD ATTARIAN and HAROLD F. WELCH

ANNUAL MEETING ADDRESS OF THE PRESIDENT

AN ENDOCRINE PROBLEM

Transcription of a Clinical-Pathological Conference

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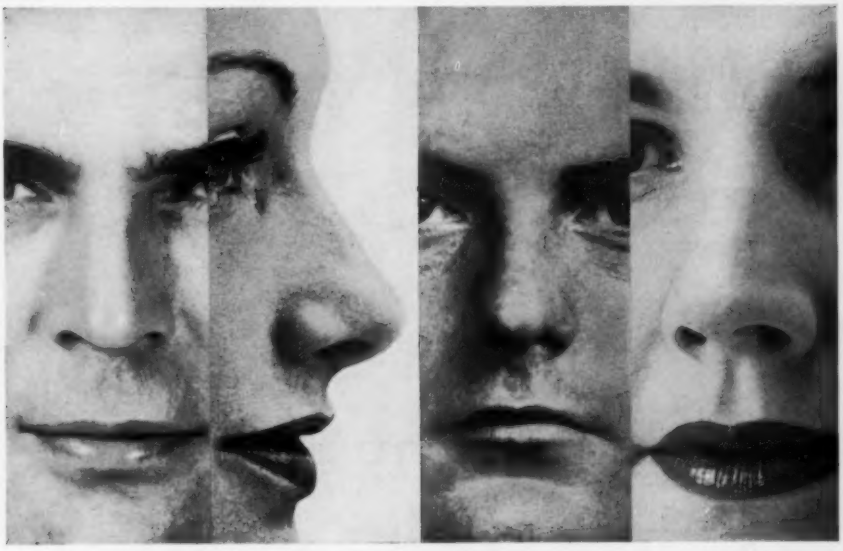

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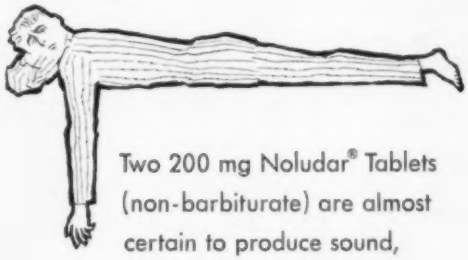
feeling 

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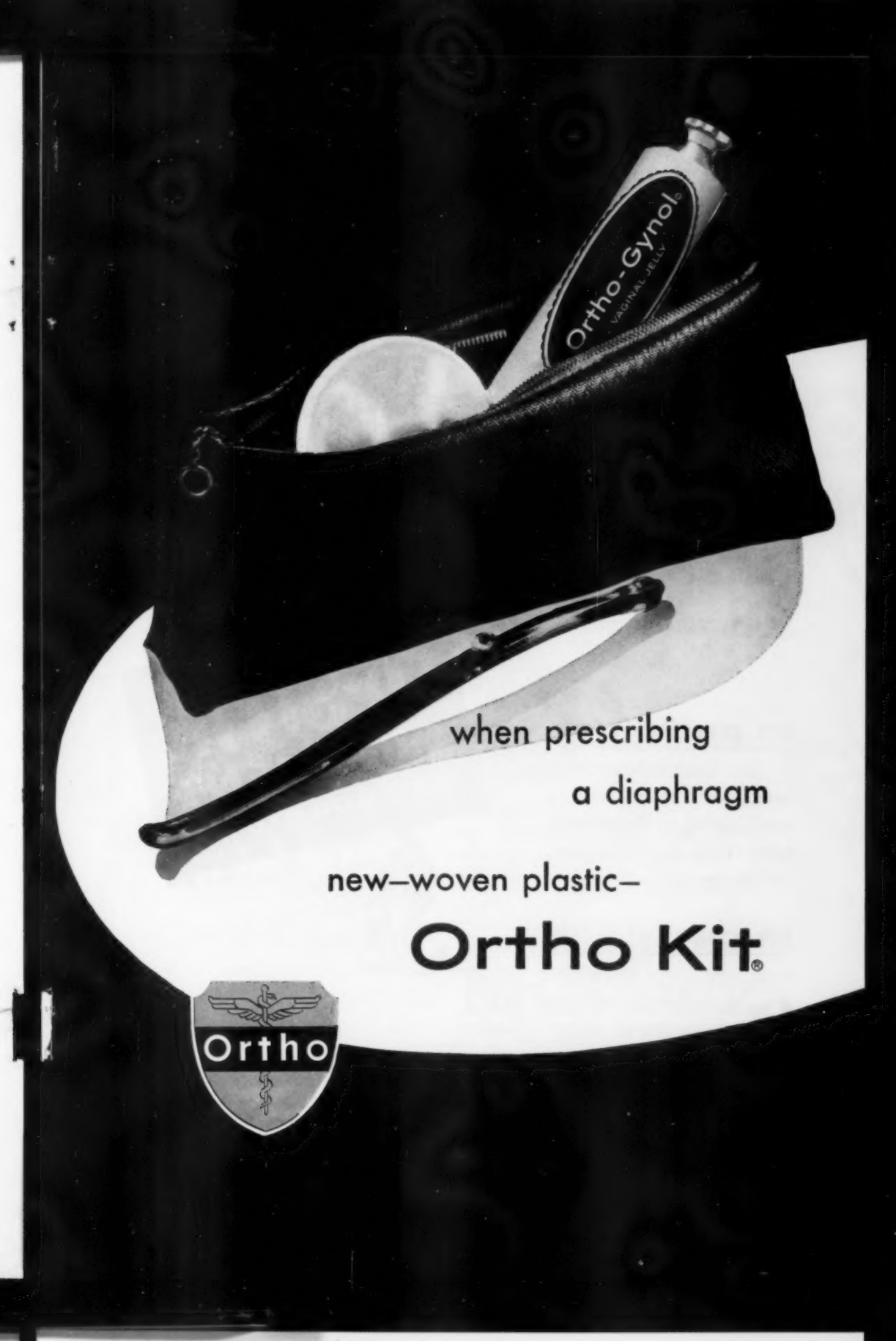
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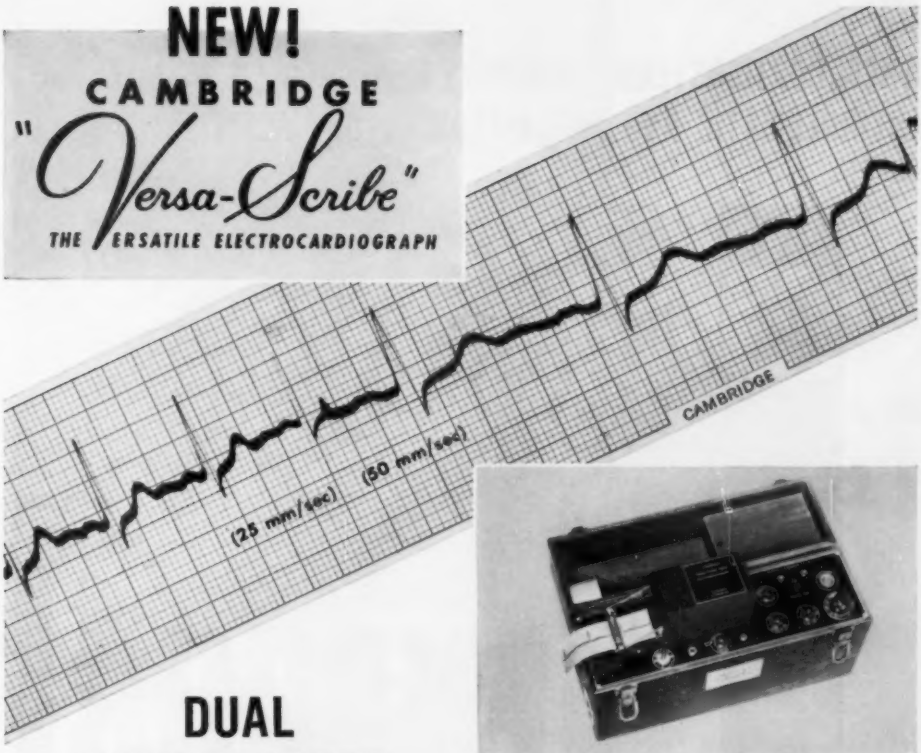

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ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.
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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 34, NO. 4 APRIL 1958

THE FUNCTIONS OF AN ACADEMY OF MEDICINE

*Address of the President**

ROBERT L. LEVY

ONCE a year, the President is expected to report to the Fellows concerning Academy activities during the preceding twelve months. In addition, if he so desires, he may indulge in a few casual remarks, preferably pertinent. My comments will be concerned with the functions of an Academy of Medicine. These will be considered first, by summarizing the program presently followed here; second, by looking at the organization and aims of comparable institutions elsewhere; and third, by taking a hasty glimpse into the future.

To give a detailed review of all that has transpired within these walls in 1957 would require an inordinate amount of time and be of little general interest. Accordingly, I have asked for brief statements from various members of the full-time staff and now present them.

SUMMARIZED REPORTS

The Director—Dr. Howard Reid Craig. During 1957, the Academy operated on the basis of a budget anticipating an income of $632,700,

* Delivered at the Annual Meeting of The New York Academy of Medicine, January 2, 1958.

an increase of $38,500 or 6.48 per cent over 1956. This figure takes no cognizance of contributions made to the Academy during the year. Expenses budgeted for 1957 amounted to $649,684, an increase of 5.16 per cent over 1956. Of this increase in costs, salaries were raised an average of 4.35 per cent over-all and supplies and materials increased 7.3 per cent. These figures do not seem out of line in view of the generally increased cost of living, services and materials. Although audited accounts, as of December 31, 1957, will not be available for some weeks, it is clear now that the Academy has operated well within its budget and will have closed the year 1957 in the black. However, unsettled world conditions and the unpredictable future of our national economy for 1958 dictate that there should be no sizeable financial expansion of Academy activities in 1958 and that we continue to operate in a conservative and economical manner.

It is important that we put our house in the best of order. To that end the President, on authorization of the Council, has appointed a committee to survey all of the functions and activities of the Academy. At the conclusion of this survey, the committee will make recommendations, to be approved and implemented by the Council, which should enable the Academy better to serve the medical profession and the community. This matter will be discussed in more detail by the President.

The only major construction during the year was the complete refurbishing of the department of photography at a cost slightly in excess of $20,000. This included the installation of new developing apparatus, new plumbing and lighting, and certain structural changes in that area. These renovations will provide facilities for greater volume and improved quality of work in photographic reproduction.

The Library—Miss Gertrude L. Annan, Librarian. The Library reports with satisfaction that for the first time in several years attendance has increased. Statistics show an addition of almost 8 per cent over the 1956 record. A survey of readers during November indicates that the percentage of Fellows using the Library is more than twice that of the previous survey of 1947. It is also of interest to note that during that month we had visitors from 17 foreign countries.

The major problem facing the Library is the critical shortage of space which every large research library must solve in this day of

an overpowering flood of publications of all kinds. It is obvious that in a few years every inch of shelf space will be crowded. To meet this emergency the Library Committee invited several medical librarians of this area to meet and discuss the possibility of a cooperative venture, such as a depository collection to hold the least used volumes. This could mean an enormous saving of space and the added advantage of cooperative collecting in certain fields where duplication is expensive and unnecessary. More complete coverage of such important material as health reports would also be made possible.

To answer an obvious need a small brochure was issued, entitled "Your Library: What Every Fellow Should Know." It is the hope of the Committee that this will make the services of the Library more easily available to members of the Academy.

The Friends of the Rare Book Room continue to enrich our collection through their generosity. The most exciting single volume given by them in 1957 is a beautiful thirteenth century medical manuscript on vellum containing the texts of several outstanding authors of the middle ages. Another extraordinary gift came from Mr. Mortimer L. Neinken—a collection of nearly nine hundred Italian broadsides of the sixteenth and seventeenth centuries. Over a thousand, of the eighteenth and nineteenth centuries, are to come in 1958. These official manifestoes all have to do with health problems, chiefly in relation to the epidemics which swept through the cities at that time. These unusual and valuable documents provide a primary source for historians.

The Committee on Public Health—Dr. Harry D. Kruse, Executive Secretary. The Committee on Public Health, having been informed that at present the majority of cases of viral hepatitis result from accidental infections from insufficiently sterilized instruments, looked into possible means of prevention. Specifications for sterilization were drawn up, and it was recommended that the Commissioner of Health undertake an educational program to inform medical personnel of the hazard and to urge them to take every precaution, particularly in the technique of blood transfusion.

At the request of the City Health Commissioner, the Committee studied the present widespread use of tranquilizing drugs. Evidence that it is a public health menace was found to be inconclusive, but the Committee suggested that the Sanitary Code be broadened so as to

accord with Federal Law with respect to prescription drugs and also to provide for control of the refilling of prescriptions.

A third problem submitted to this Committee was the need for minimum standards to be applied to medically directed psychiatric clinics. The Committee recommended that all such clinics be licensed by the state and it then specified standards of licensure and operation for them.

An *ad hoc* committee, representing the organizations carrying on blood activities in New York City, recognizing that an unsatisfactory situation exists, requested the Committee on Public Health to survey the procurement, distribution, and utilization of blood throughout New York City, and to recommend measures for improving the present status. With gratifying and remarkable cooperation, every agency except one provided data on its activities. Thus it was possible to account for 100 per cent of all the blood used and, probably, not less than 90 per cent of the blood collected in New York City during 1956.

On the basis of these data the Committee made 60 specific recommendations. It was the judgment of the Committee that it was necessary to develop a community interest in blood and to create a service dedicated to the public weal; and that to achieve that desirable position, the entire blood enterprise should be put under the aegis of an organization established on a community scale. In the existing framework the most workable proposal that would bring about a degree of centralization would be the formation of an organization representing all the existing enterprises and the centralization of parts of the operation. Thus, New York City could achieve many of the benefits of central direct management without sacrifice of its already-established individual agencies. Hence, the Committee's first recommendation was that all of the blood agencies in New York City which participated in the survey formally organize, on a permanent basis, a community body concerned with blood. The remaining recommendations, covering all aspects of blood activities, pertained to the functions and program of the community organization and its administrative and operational center, and the responsibilities of the individual agencies.

The Committee on Medical Education—Dr. Robert L. Craig, Executive Secretary. The following scientific programs were arranged:

1. Stated Meetings. In some instances these were planned in co-

operation with the various Sections, the Committee on Public Health and other organizations, such as the James Ewing Association.

2. Monthly Panel Meetings for the General Physician.

3. The Postgraduate Week. The topic this year was "Research Contributions to Clinical Practice". Both format and content represented continuing experimentation. The most marked change from previous years was the reduction in the total duration of the sessions from two weeks to one week. Fifteen lectures on varied subjects were given during a five-day period and a panel meeting was held each afternoon. The Scientific Exhibit was on display for two weeks. Excluding visitors to the Exhibit, the total attendance at the lecture and panel meetings was about the same as last year, namely 1,655 in 1956 and 1,680 in 1957.

The Bernard Sutro Oppenheimer Lectures, dealing with studies of the cardiovascular system and its disorders, were inaugurated. The first lecture was given by Dr. Dickinson W. Richards, Jr., who spoke on "Some Problems in the Physiology of Dyspnea". The second lecture will be given in April of this year by Dr. Gunnar Biörck, of the University of Lund, Malmö, Sweden.

Under provisions of the Bowen-Brooks Fund, the Committee awarded one scholarship in the amount of $4700 for study abroad for the academic year 1958-1959.

Three sub-committees are now engaged in assessing current Academy educational activities and drawing plans for future efforts in various areas of postgraduate medical education.

The Bureau of Medical Education has continued to answer many requests, from both the medical and lay public, for information on a great variety of subjects relating to this field.

The Committee on Medical Information—Dr. Iago Galdston, Executive Secretary. The Committee issued 40 press releases and reviewed 116 manuscripts submitted by 89 different publications in the United States. The Bureau and its consultants dealt with some 11,000 inquiries.

A pilot study was launched, having the title, "Whither Medicine". To carry this forward, grants totalling $12,500 were obtained from the Commonwealth Fund and an anonymous donor. The material eventually will be published.

Under the aegis of the Committee three books appeared, namely,

Medicine in a Changing Society, *On the Utility of Medical History*, and *Freud and Contemporary Culture*. Two additional manuscripts have been prepared, representing the transactions of conferences.

The FM Program "For Doctors Only" has been continued. There have been two series, one in which the contributors were British, the other in which the speakers were French scientists.

The Eastern States Health Education Conference, held in April, was devoted to the subject, "The Family in Contemporary Society".

The calendar year saw the completion of the 22nd Series of "Lectures to the Laity" and the initiation of the 23rd Series. The latter is concerned with the theme, "Medical Progress in the Offing". The first talk in the new series was delivered by Dr. Hans Selye, of Montreal, who spoke on "The Stress of Life".

In cooperation with the Rockefeller Institute for Medical Research, arrangements have been completed for the Annual Meeting of the American Association for the History of Medicine. The Academy and the Institute are to serve as hosts to the Association.

The Bulletin—Dr. Robert L. Craig, Secretary and Editor. The Bulletin has continued to publish original articles which have been presented at various Academy functions as well as abstracts submitted by the Section on Microbiology and the New York Pathological Society. In addition, a number of transcripts of panel meetings have appeared.

The Bulletin is distributed to all Fellows of the Academy, to 1400 paid subscribers and to 350 Library exchanges.

The Committee on Sections—Dr. Robert L. Craig, Secretary. The twelve Sections of the Academy have continued their meetings though there is an increasing tendency to reduce the number held. On several occasions two or more Sections have combined to arrange the program of Stated Meetings. The average attendance at Section meetings increased during the past year by 30 per cent.

The Committee on Admission, under the chairmanship of Dr. Philip D. Wiedel, has worked faithfully to maintain the high standards of character and professional attainment required of those who seek to become Fellows.

The Trustees, with Dr. Orrin S. Wightman as Chairman, Dr. Shepard Krech as Treasurer and Mr. Arthur A. Eberle as Comptroller, are responsible for the sound financial position of the Academy, as indicated in the report of the Director.

It may fairly be said that the year has been one of fruitful activity.

Character and Goals of Some Comparable Organizations

It seemed of interest and, perhaps profitable, to inquire into the activities of other organizations with aims similar to our own. To obtain the necessary information requests were sent to a number of executive directors for available reports, pamphlets and journals. These, together with some of the letters received in reply, comprise the background for comparison.

The institution which appears to resemble most closely the New York Academy is the *Royal Society of Medicine of London.* Founded in 1805, it is privately supported and is greatly aided, financially, by various pharmaceutical firms. The Society consists of nearly 10,000 Fellows, Members and Associates, both British and foreign, of whom 1,600 live overseas.

The Society has its own building in which the library is housed and scientific meetings are held. The proceedings of the meetings are published in a monthly Journal. An active photographic unit undertakes medical photography and cinematography. Non-residential club services are provided for those using the library and attending scientific meetings; a restaurant and common rooms are available.

The Society needs additional funds to enable it to extend its activities and, particularly, to increase the facilities of the library. It is hoped that financial assistance will make possible the establishment of a "Domus Medicus"—a Hall of Residence for foreign and provincial doctors who come for consultation and research. Support is desired also for the support of two-way visits between the Fellows and visitors from abroad. Discussions have been held concerning the formation of a Section of Industrial Medicine, in order to give to this subject an academic standing which, so far, it has not attained in England.

The Institute of Medicine of Chicago, incorporated in 1915, operates along lines similar to those followed here. It has no home of its own, however, and operates from offices in the John Crerar Library

Building. Membership is by invitation only and the present policy seems to indicate that the number of members will remain under 700, although there is no fixed limit.

Numerous committees are concerned with public health, with convalescent and chronic care, with medicolegal problems and grants for special projects. The Proceedings of meetings are published as a journal and there are endowed lectures, fellowships, prizes and research funds. There is close cooperation with the local Welfare Council; some 20 societies in the area are affiliates.

The Institute is privately endowed and supported. Its business affairs are managed by a Finance Committee composed in part of Citizen Fellows.

The Academy of Medicine of Cincinnati was organized in 1857. According to a letter from the Executive Secretary, its activities are carried on by four corporations. The Academy of Medicine is a non-profit corporation. The Cincinnati Journal of Medicine is a corporation for profit, the Physicians' Business Bureau is a corporation for profit and the Cincinnati Health Museum, a supplemental corporation to the Academy, is also a non-profit corporation. It maintains its own telephone service and publishes a two-page monthly newsletter called the Acadogram, as well as the Cincinnati Journal of Medicine and an annual directory of members. A council and 39 committees perform the usual functions of such an organization. The Academy does not have its own building or library. Its activities are combined with those of the Hamilton County Medical Society.

It is clear that, in structure and aims, there is wide variation in different localities. No additional information of special interest was obtained by further sampling, although material from numerous other sources was examined. It does appear, however, that almost all of the smaller organizations, some of which are designated as Academies, actually operate as county medical societies.

A Glimpse Into the Future

The New York Academy of Medicine was founded in 1847. Its present functions, as defined by the Constitution, are "the advancement of the science and art of medicine, the maintenance of a public medical library and the promotion of public health and medical

education". These are praiseworthy aims, but the phrases used allow of broad interpretation. In other words, they are qualitative terms; as physicians and scientists we should be concerned with the quantitative approach.

Those of you who have read the *Bulletin* for October 1957 or the Grey Folder for November, are aware that all of the affairs of this Academy are now undergoing careful scrutiny. Adaptation to the modern medical climate may well require revision of viewpoint, of organization and of operational procedure, so that the goals set shall be achieved in the most economical and effective manner. To accomplish such a searching survey, eight subcommittees have been appointed, each with its own specific area to cover and each with its own chairman. The over-all chairman of the Survey Committee is Dr. William Barclay Parsons; he and the subcommittee chairmen constitute an Executive Group. A report at this time cannot contain final conclusions or recommendations, for the work is still actively in progress. Since last April, however, many spirited meetings have been held and, in the light of what has emerged from them, I will try to summarize the current status, with reference to each subcommittee.

Administration: Dr. Marcus D. Kogel, Chairman. This report will have to be integrated, in detail, with that of each of the other subcommittees, because administration involves every activity of the Academy. All department heads are being interviewed. One of the questions being considered is the advisability of engaging the services of a management concern to operate the building and handle its nonprofessional personnel. It seems likely that such an arrangement would cut costs.

Building and Plant: Dr. Condict W. Cutler, Jr., Chairman. Inspections of the entire establishment have been made with a view to improvements and economy of operation. Because of urgent need, the subcommittee already has made a specific recommendation which was promptly approved for immediate action by the Trustees at their December meeting. It was decided to remodel and redecorate the cafeteria on the fifth floor, and purchase new equipment. A contract has been signed with a reliable concessionaire, who will supervise the operation and will furnish food and staff. Work should begin

shortly. The same firm will serve Academy dinners and will arrange for bar service; we can buy and store our own liquor at a considerable saving. Funds for this entire undertaking are available.

The Bulletin: Dr. Louis J. Soffer, Chairman. Content, source of material, its character and quality, as well as business operations, are under discussion.

Finance: Dr. Henry N. Pratt, Chairman. Three laymen, Mr. Montgomery B. Angell, Mr. George N. Emory and Mr. Henry S. Sturgis, all experienced in the field of finance, are serving as members of this subcommittee and are reviewing the Academy's investment portfolio. It is probable that a recommendation will be made to employ a management consultant firm, Cresap, McCormick and Paget, to go over the internal financial operations. This firm helped materially with the Academy's recent Study of Blood Procurement, to which reference already has been made.

The Library: Dr. George Rosen, Chairman. Ours is one of the finest and largest medical libraries in the world and is well run. Is it overstaffed? Is the budget excessive or should its facilities be expanded? In what ways can service be improved? The establishment of a deposit library, to be operated in cooperation with other medical institutions in the city, is under consideration.

Medical Education: Dr. Dickinson W. Richards, Jr., Chairman. It is apparent that the present program of postgraduate education is not in keeping with the times and, more particularly, is not suited to the requirements of a large city in which there are six medical schools, each with affiliated teaching hospitals. The solution of the problem is not readily at hand. It has been suggested that there might be a three-pronged approach with appeal to research workers, to specialists and to general practitioners. The Section meetings must be better integrated with the general educational scheme.

Medical Information: Dr. John Garlock, Chairman. The deliberations of this subcommittee have not yet been divulged. It is known that the cost of the many projects sponsored by the Committee on Medical Information is being scrutinized.

Public Health: Dr. Duncan W. Clark, Chairman. The report of this subcommittee is said to be almost complete. The Committee on Public Health has done outstanding work and it seems unlikely that any radical changes in its program will be suggested.

These fragmentary remarks cover all that can now be said. The Survey Committee, probably by next spring, will submit its findings and recommendations to the Council for discussion, approval and action. Those who are giving time and thought to this project are proceeding with enthusiasm and vigor. That the results of their labors will increase the usefulness of the Academy to its Fellows, to other physicians and to the general public, seems assured. Throughout the Survey, the initiative and help of the Director, Dr. Howard Reid Craig, have been invaluable. In this, as in every phase of Academy affairs, it is to him that all turn for guidance.

By way of conclusion, and at the risk of offending the more literal-minded, I shall venture a short excursion into the realm of metapsychical phenomena. A printer's error started this train of thought. On the first page of the Academy Bulletin for April 1957, the usual heading which, for decades, has read "Bulletin of The New York Academy of Medicine", appeared as "Bulletin of The *New* Academy of Medicine" (italics mine). By an odd coincidence, it was just at this time that the Survey, designed for modernization, was getting under way. Can this combination of circumstances be regarded as a good omen? Future developments will tell; but there is every reason to look forward with confidence.

TIME—A FOURTH DIMENSION OF PATIENTS*

The Anniversary Discourse

C. SIDNEY BURWELL

Samuel A. Levine Professor of Medicine, Harvard University Medical School; Physician to the Peter Bent Brigham Hospital and Visiting Physician to the Boston Lying-in Hospital

IT IS a great honor and pleasure to be asked to give the Anniversary Discourse to The New York Academy of Medicine. I am grateful for the opportunity.

Your distinguished President, when he first spoke about this, imposed certain restrictions on the speaker. The most definite of these clearly had to do with the length of the discourse, but he also suggested that this was not an occasion for the presentation of technicalities of research, but rather for a discussion of some broad principle, applicable to medicine but dealing with its philosophy rather than with its details. It has occurred to me, therefore, to present for your brief consideration an aspect of patients which is obvious enough but seldom discussed—namely, the factor of time or, more specifically, *the time in his own life when the patient is seen* as part of his description.

There is wide acceptance of the fact that physiological differences exist between different people. The Declaration of Independence says clearly "All men are created equal" but this need not, and should not, be taken to indicate that these equals are identical. Human beings, equal in fundamental importance as individuals, are indeed diverse in their characteristics, and those diversities have important significance for the occurrence, the progression, and the management of disease and disability.

This is all obvious, but it is not always as clearly understood that a given individual observed at one time may exhibit sharp differences as compared with himself at another time. Perhaps I can illustrate this concept by reminding you of a musical comedy hero who played his

* Given at the Annual Meeting of The New York Academy of Medicine, January 2, 1958.

role so long ago that I am afraid few of you here had the pleasure of seeing him. I recall that he came on the stage to find a sideboard laden with drink, poured himself a libation, consumed it, and then said, "This makes a new man of me." Following this his face became thoughtful and then brightened as he said, "Give the *new man* a drink." These observations showed clearly that he understood that an organism could change with the passage of time and with the alteration of circumstances.

Following the classical work of Claude Bernard in the middle nineteenth century and of L. J. Henderson, Walter Cannon, and others in recent years, we are all strongly and properly impressed with the beautiful and generally effective mechanisms of homeostasis. These mechanisms have an extraordinary capacity to maintain the internal environment as a relatively stable one. It should be remembered, however, that in certain situations the levels of various bodily functions are reset at new points much as we set the thermostats in our houses at different levels to meet new conditions. Under these circumstances, homeostatic mechanisms continue to operate, but the definition of the internal environment has been altered.

Some of the conditions which lead to a change in the internal environment are imposed from without, and one can think of many instances in which disease establishes a new level about which a given function may fluctuate. Often, however, such changes occur as parts of normal healthy life, and it is with these that we are to be concerned tonight. I will ask you to consider in a somewhat superficial and postprandial manner some of the changes in the physiology of the human organism associated, first, with the aging process, second, with the state of pregnancy, and, third, with that beneficial and recurrent phenomenon called sleep.

The changes that occur with these natural events are extensive enough and impressive enough to make it fair to say that during these states we are actually dealing with a different kind of organism. These changes are often sufficient to alter the reactions of the body to such a degree that they influence for worse or for better the incidence and course of disease.

There is certainly nothing new about the point of view that *external* events can alter the responses of the human organism at different times. This belief is clearly embedded in folklore as well as in medical litera-

ture. In the "Golden Bough" Frazer refers to the deep impression made on dwellers near the sea by the ceaseless ebb and flow of the tides. He says, "The belief that most deaths happen at ebb tide is said to be held along the East coast of England from Northumberland to Kent."

Tonight, however, we are concerned not with influences, whether chemical, bacteriological, or sidereal, which are imposed from without, but with those imposed by fundamental, and to some degree, built-in rhythms which are part of the organism's original equipment. We have chosen as our examples aging, pregnancy, and sleep. In discussing these we shall be concerned primarily with physiology, although as in most conversations among doctors, medicine will keep breaking in.

The fact is familiar to all that growth, development, and aging do, over the years, profoundly alter organisms. Dr. John Lovett Morse used to say to his students when he taught pediatrics in the Harvard Medical School, "A baby is not a little man." He wanted us to learn, I think, that infants and children are qualitatively and quantitatively different from young adults and from the aged. We know that growth, development, and involution produce changes in the physiology of the human organism, quite aside from wear and tear. We can all think of examples of the differences that exist in these groups. In youth the oxygen consumption per square meter is higher and it tends to fall progressively with advancing age. The processes of growth and development and the youthful expenditures of energy call for more food than in later years. One definition of youth—I think from "Three Men in a Boat"—is based on the experiment of offering a large soggy bun to the subject fifteen minutes before dinner. If it is accepted the diagnosis of youthfulness may be made.

Obviously the amounts and relationships of hormones are different in youth and age and it is not surprising that the same person at different ages is a different organism in his response to disease. Think, for example, of the variations in the course of acute rheumatic fever, or acute nephritis, or measles when these disorders occur in different age groups. When pernicious anemia or gout or diabetes develops in members of susceptible families, they may develop because of identifiable trigger factors or special varieties of wear and tear. However, in many patients they develop because of changes in metabolism associated with involution and not due to specific external precipitating factors.

When Shakespeare wrote, "Crabbed age and youth cannot live

together" he was, I think, not only pointing out that youth is full of pleasures and age full of care, but also reflecting an old observation that young and old are different kinds of people and may not be happy or well in identical environments. At the same time they may be very good for each other and may indeed be essential for each other.

Some of this difference between old and young appears to be a difference in the rate of living or the rate of energy expenditure. You will remember that at one point in Lewis Carroll's *Through the Looking Glass* the Red Queen seized Alice by the hand and they ran rapidly for a considerable period. At the end of this period Alice observed that they were still under the tree where they had started. She expressed surprise at this and observed that in her country if you ran rapidly for some time you were apt to get somewhere. The Red Queen replied that Alice must come from a slow sort of country and that in her country you had to run that fast to stay in the same place and at least twice that fast if you wanted to get anywhere. Experience indicates that children run, metabolize, and heal their wounds faster than their elders; physiology does not say that by so doing they are necessarily going to get anywhere except to older decades of life.

A more specific and better defined example of variation in a given organism with the passage of time is seen in the fascinating and elegant adjustments that are made in the physiology of a woman when she becomes pregnant. The implantation of the fertilized ovum establishes a new set of requirements. The mother responds by becoming a different organism although certainly and happily still the same woman. As my colleague, Dr. James Metcalfe, has written, "Animal reproduction is enacted by inconvenience on the part of the mother, tenacity on the part of the foetus, and cooperative ingenuity on the parts of both." By this cooperative ingenuity, the fetus is supplied with nutriments, oxygen, and various complex chemical substances such as enzymes, and mechanisms are developed for the disposal of the end products of fetal metabolism.

The adjustments on the part of the maternal organism involve many aspects of physiological function. One change which I was not aware of until relatively recently is an increase in acuity of the sense of smell. To a few women in our experience this is so marked as to be annoying, and in one of our patients this troubling sharpening of sense of smell has occurred in each of four pregnancies. It is interesting to find an

example of this in another species referred to by Chamberlain in his charming book *Bouquet de France; an Epicurean Tour of the French Provinces*. The people of Périgord, it appears, use pigs to seek the truffles which constitute a major resource of this part of France. The pigs find these underground treasures by smelling them, and Chamberlain observes "Small expectant sows are the most competent sniffers."

As the fetus and placenta develop, there occur in the maternal organism extensive alterations in circulation, in ventilation, in the kind and amount of hormones, and in many other mechanisms. We may select as examples more nearly relevant to our discussion some of the alterations in circulation and in ventilation. The volume of blood increases and the cardiac output rises. It is not surprising that during pregnancy these systematic increases in the volume of blood and the cardiac output are observed since it is obvious that the mother's circulation has assumed the new and important duty of transporting materials to and from the fetus. The changes in the circulation are to a considerable degree predictable and have major and sometimes vital implications for the course of heart disease in pregnant women.

Equally impressive changes occur in respiration. One expects that in association with the increased oxygen consumption of the mother there should be an increased ventilation since, as Sherrington says, "The foetus breathes through its mother's blood." It is interesting, however, that the ventilation of the pregnant woman increases sooner and increases more than her oxygen consumption. She actually shows alveolar *hyperventilation* so that the level of carbon dioxide in the arterial blood falls, usually from about 40 mm. to about 30 mm. Hg. This cunning adjustment of carbon dioxide tension permits the fetus to develop at non-toxic levels of carbon dioxide pressure in spite of the substantial gradient of this gas across the placenta.

Now, to change the level of arterial carbon dioxide tension for this nine-month period, some mechanism must be established by the fact of pregnancy. It should be noted that the change in tension takes place early in pregnancy before the oxygen consumption rises measurably, and the change is maintained throughout the course of pregnancy, and that by a few days after delivery the alveolar ventilation has fallen to normal levels in relation to oxygen consumption and the CO_2 has risen to the non-pregnant level. This extraordinary and, from the point of view of the fetus, apparently beneficial adjustment, appears to be due

to actions of progesterone on the respiratory center. This substance is appropriately produced, at least in large part, by the very organ that makes it necessary—namely, the placenta.

Angus MacDonald wrote the first book in English on the relations between heart disease and pregnancy in 1878 and he referred to an observation on the ventilation in pregnant women which is against the expectations of common sense—namely, that the vital capacity of the lungs is not diminished by pregnancy in normal women. In spite of the large tumor filling her abdomen and elevating her diaphragm, some increase in the total lung capacity, plus some invasion of the residual air, enables the pregnant woman to maintain a normal vital capacity and sometimes a slightly enlarged one throughout the course of her pregnancy. The fact that normal women maintain a normal vital capacity during pregnancy does not mean that the tumor of pregnancy is unimportant since in women with kyphoscoliosis and a more rigid rib cage a diminution of vital capacity, sometimes enough to be hazardous, can take place as the uterus increases in size. The maintenance of a normal vital capacity does mean that the pregnant woman by a beneficent provision of nature has increased the capacity of the pulmonary bellows to meet the new demands of a special situation.

Something about pregnancy, perhaps some aspect of the metabolism of estrogens, has profound effects upon the blood vessels of the maternal body. During much of pregnancy we are accustomed to observe a fall in the diastolic blood pressure. The vessels in certain areas of the skin become visibly dilated and the distribution of blood to the skin is obviously altered. In some women changes actually occur in the structure of arterial walls,—changes sufficiently severe so that arterial rupture takes place. This catastrophe when it occurs usually affects arteries which were already abnormal before pregnancy. As examples, consider the dissection of the aortic wall which may take place during pregnancy in patients with coarctation of the aorta; the rupture of berry aneurysms of the circle of Willis, which may occur during pregnancy and the considerable number of ruptures of splenic artery aneurysms which have occurred in pregnant women. These catastrophies do not as a general rule occur under the stress of labor (in spite of a tradition to this effect), but occur most often at the seventh or eighth month of pregnancy. The reasons for this are not yet clear, but the documents are impressive.

In general, changes in maternal physiology occurring with pregnancy are favorable to the survival and development of the fetus. Some of them impose discomforts or hazards upon the mother. When alterations in physiology of the magnitude we have described occur during pregnancy, it is not surprising that a woman when pregnant may react to disease quite differently than when she is non-pregnant. Doctors are familiar with the changes that may occur during pregnancy in the manifestations of rheumatoid arthritis, of diabetes, and of heart disease. Women with long-standing symptoms of duodenal ulcer may become symptom free with the onset of pregnancy. On the other hand, there are women with evidence of duodenal ulcer who bleed from it during pregnancy and not at other times. Those of you who read novels or go to the theatre know from those experiences that fainting may occur during pregnancy and may indeed be the event that calls attention to its existence and announces it to the frightened mother or the happy father. It is now also known that there are patients who have fainted at intervals when not pregnant and who have the curious experience of being free of syncope during pregnancy. In the light of these and other examples it is easy to see and unnecessary to say that to care for disease in a pregnant woman it is essential to understand the physiology of pregnancy as well as that of disease.

The final example of my simple thesis is a phase of life which has been studied too little. This is *sleep*—that agreeable but often forgotten state in which a considerable fraction of our lives is necessarily spent. Sleep is necessary to survival and it tends to recur regularly. Significant physiological changes accompany it and with some of these we shall be concerned. We are discussing what is called natural sleep, not hibernation or narcolepsy or coma. Everyone is aware of sleep as part of life and many observers of life have described it eloquently. Henley wrote:

> "Night with her train of stars
> And her great gift of sleep."

Sir Philip Sidney:

> "Come Sleep! O sleep, the certain knot of peace,
> The baiting place of wit, the balm of woe,
> The poor man's wealth, the prisoner's release,
> Th' indifferent judge between the high and low."

Shakespeare understood some of its physiological effects:

". . . the innocent sleep.
Sleep that knits up the ravell'd sleeve of care,
The death of each day's life, sore labor's bath,
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast."

Not all the references are so filled with approval of sleep. It is also called death's counterfeit and death's twin brother. It should not be called these nor should it be referred to as a state midway between death and life. Sleep is not partial death; it is a different kind of life.

This life is not without its special brand of consciousness, and the study and interpretation of dreams have fascinated mankind for generations. It is said that Dryden supped on raw flesh to obtain splendid dreams, no doubt as a basis for splendid poetry, and the author of "Mysteries of Rudolpho" is said to have eaten the most indigestible substances for the purpose of filling her sleep with phantoms of horror —an occupational hazard for authors.

Sleep is in general admirable, pleasant, and useful. Cervantes had Sancho Panza speak wisely when he said, "We count our blessings on the man who first invented sleep." A modern author, John Godfrey Saxe, has recorded Sancho Panza's attitude and added some comments of his own in the following stirring verse:

" 'God bless the man who first invented sleep!'
So Sancho Panza said, and so say I:
And bless him, also, that he didn't keep
His great discovery to himself; nor try
To make it—as the lucky fellow might—
A close monopoly by patent right!

"Yes, bless the man who first invented sleep
(I really can't avoid the iteration)
But blast the man with curses loud and deep
What e'er the rascal's name, or age, or station
Who first invented and went round advising
That artificial cut off—Early Rising."

However pleasant these comments and reflections of others may be, they are not our present duty. Let us consider some characteristics of

sleep and some of the physiological changes which are known to accompany it. Many of the characteristic physiological differences between the waking and sleeping individual come on rapidly with the change from one to the other. Some of them occur, as we shall see, in a matter of seconds. Most of the changes that we know about are not the cause of sleep. They are associated with the fact of sleep. In a sleeping person, for example, there is a widespread muscular relaxation, a diminution in body temperature, and characteristic changes in the electroencephalogram. Oxygen consumption falls and so does the production of CO_2. In spite of diminution in the production of CO_2, the level of carbon dioxide in the alveolar air and in the arterial blood rises. It rises significantly, as much as 5 or 10 mm. Hg. This is just the opposite of what occurs in the pregnant woman. It is another example of a natural event leading to the establishment of a new equilibrium in a vital and consistent physiological measurement.

This rise in carbon dioxide tension is due to alveolar *hypo*ventilation as the fall in carbon dioxide tension in pregnant women is due to alveolar *hyper*ventilation. The hypoventilation of sleep is apparently related to an alteration in the sensitivity of the respiratory center to the stimulus of carbon dioxide. This change in sensitivity can be demonstrated by observing the effects of inhaled carbon dioxide on sleeping persons. An interesting aspect of this matter is that this change in sensitivity occurs with amazing rapidity and is demonstrable a few seconds after the onset of sleep.

This diminished sensitivity of the respiratory center during sleep is probably one of the reasons why periodic respiration occurs in some normal people during sleep, and why during sleep patients with heart or pulmonary disease may show a marked accentuation of a previous existing periodicity. Indeed, sleep may be a time of increased abnormality in patients with some varieties of disease, especially those who already have an elevated carbon dioxide tension. When to the elevated carbon dioxide of disease is added a further elevation due to sleep, a further and potentially harmful depression of the respiratory center may ensue.

Physicians have long been interested in the variations and the manifestations of disease between sleeping and waking. One example will suffice. Paroxysmal nocturnal hemoglobinuria is a disease characterized by the presence of abnormal erythrocytes which undergo hemolysis

more easily than do normal red cells. This increased hemolysis takes place under special conditions. The most frequently recognized situation associated with increased hemolysis is the sleeping state. These patients usually show a peak of plasma hemoglobin levels between one and four o'clock in the morning, and the morning urine contains the largest amount of the hemoglobin which they excrete during a 24-hour period.

If these patients sleep during the day and work during the night, they reverse the pattern of hemolysis so that now the major portion of hemolysis takes place during the daytime hours.

Cells from these patients, studied *in vitro*, hemolyze in acid media, but it has been demonstrated that the modest respiratory acidosis that develops during sleep is not responsible for the increased hemolysis during this state. Nor is the increased carbon dioxide of sleep responsible since much higher levels of CO_2 can be imposed on the red cells without inducing hemolysis. The metabolic change which produces the disorder is not known, but it is something which accompanies sleep and makes us want to know much more about the physiology of this important part of our lives.

Summary

These rather rambling reflections may remind us that as physicians we deal not with an invariable or monotonous organism, but one which while basically stable still shows fascinating, important, and to some degree predictable variations. These variations are not in the eye of the beholder, but in the patient. In our interpretation and management of disease, we are accustomed to recognize and control many factors in the external environment, such as temperature, dust, pathogenic organisms, insects, noise, the gas content of the inhaled air, and the ambient emotions. We have also to realize that comparable variations occur in the internal environment due to changes in the pattern of homeostasis associated with such natural events as growth, development, pregnancy, and sleep.

Certain examples of such changes have been presented. It has been possible to show, for example, that the carbon dioxide tension of the arterial blood falls during pregnancy and rises during sleep. The first change is apparently based on a hormonal mechanism; the second on a neural mechanism. As far as the available evidence goes, the aging

process is not associated with comparable changes in carbon dioxide tension although it is associated with progressive changes in certain quantitative aspects of ventilation. This presumably means that the basic mechanism for the maintenance of a more or less standard level of carbon dioxide in the arterial blood is not altered by the progressive changes of involution, whereas the non-permanent changes in pregnancy and sleep do alter the controlling mechanism so as to reset this level for the duration of these states.

Therefore, as the mathematician may think of time as a fourth dimension added to space, we, as physicians, may think of time as an additional definition often significant in patients.

This discussion has emphasized the factor of change in the human organism. It would not be fair to conclude it without reminding you that the changes we have been discussing happily occur without destroying identity. Let us be thankful that this durable and tenacious organism, which is the basis of our life and happiness, not only exhibits the fascinating changes we have discussed, but it exhibits also a wonderful and vital continuity. In the changes imposed by the natural events of life, individuality is not lost and our friends are still our friends though they may be old, or pregnant, or asleep.

CITATION AND PRESENTATION OF THE ACADEMY MEDAL* TO ALPHONSE RAYMOND DOCHEZ, M.D.

ROBERT L. LEVY

President, The New York Academy of Medicine

THE Academy Medal, for which an endowment was provided in 1928 by Dr. Samuel McCullach, is awarded, at the discretion of the Council, for distinguished service in medicine. The recipient this evening, Dr. Alphonse R. Dochez, is the eleventh physician to be so chosen in the course of twenty-eight years.

There have been many evidences of the esteem in which Dr. Dochez is held by his colleagues. Among the honors bestowed upon him was the Kober Medal of the Association of American Physicians, in 1949. The presentation was made by his close friend and co-worker for forty years, Dr. Oswald T. Avery who, in the course of his remarks, had this to say: "What Dr. Dochez has done is well known; but how he did it is less easy to define. The results of his work have not only theoretical value but have found direct application in clinical teaching and medical practice." These few words indicate the wide scope of Dr. Dochez's influence.

Shortly after graduation from the Johns Hopkins Medical School he was appointed to the staff of the Rockefeller Institute, where he spent eleven years. Here, with Gillespie he established the biological classification of pneumococci into specific types. He developed methods and techniques for the production and clinical use of anti-pneumococcus serum, at that time the only known form of specific therapy for lobar pneumonia. His work laid the foundation upon which rests knowl-

* Presented at the Annual Meeting of The New York Academy of Medicine, January 2, 1958.

ALPHONSE RAYMOND DOCHEZ, M.D.

edge subsequently developed concerning the immunochemistry of the pneumococcus.

During World War I, Dr. Dochez served, with the rank of Major in the Medical Corps of the United States Army, as a member of a committee appointed by the Surgeon General to study epidemics of acute respiratory disease due to hemolytic streptococci. The results of these observations showed that a majority of the strains investigated comprised six serological types. This demonstration furnished the basis for later studies of streptococcal diseases and their sequelae.

In the fall of 1919, Dr. Dochez returned to Baltimore as Associate Professor of Medicine at Johns Hopkins University. Here he initiated his studies of scarlet fever, which were continued when, two years later, he moved to New York with Dr. Walter W. Palmer, to establish the first full-time Department of Medicine at Columbia University. Together with the Dicks, Dochez may be credited with establishing the hemolytic streptococcus as the cause of scarlet fever.

The problem to which Dr. Dochez next devoted several years was the etiology of the common cold. With his associates, he succeeded in isolating a virus from the nasal washings of patients which caused, in chimpanzees, the characteristic symptoms of a spontaneous cold in man. These results, with their implications, have since been confirmed and extended.

Officially, Dr. Dochez is now retired. But he still visits the hospital and laboratory, where his wise counsel is always available and frequently sought.

Those who have known Dr. Dochez most intimately have been impressed by the absence of hurry in all of his activities. His investigations have been characterized by thoughtful planning, meticulous care in their execution and critical appraisal of their significance. Again, in the words of Dr. Avery, he never engaged in "purposeless rivalries or competitive research".

I cannot resist injecting one short personal note into these remarks. In February, 1919, I began service as Resident Physician at the Hospital of the Rockefeller Institute. On the first morning, Dr. Rufus Cole, the Director and my new chief, took me on a visit to the wards and laboratories. The tour ended in the doctors' lounge. There, on a couch, with eyes closed and hands clasped across the chest, lay a quiet figure, apparently asleep. This picture of Dr. Dochez is one which I

have never forgotten. For I was to learn that physical inactivity could mask creative thinking in one whose mind was tireless in its search for new scientific truths.

In one of his lectures on "Heroes and Hero-Worship", Thomas Carlyle wrote: "I should say *sincerity*, a deep great, genuine sincerity, is the first characteristic of all men in any way heroic. . . . A little man may have this, it is competent to all men that God has made: but a Great Man cannot be without it."

Dr. Dochez, you are one of our Great Men in Medicine. You have made outstanding, fundamental contributions. You have stimulated and encouraged students and colleagues, not only as a scientist but as one who, by example, has embodied honesty of purpose. For all of these reasons, the Academy takes pride in paying tribute. I feel privileged, as President, to present to you this Medal as a symbol of our affectionate regard.

CITATION AND PRESENTATION OF THE ACADEMY PLAQUE* TO MR. CHARLES C. MORCHAND

HOWARD REID CRAIG

Director, The New York Academy of Medicine

IN 1924, a young man, recently out of college, had set himself up on a small scale in the printing business on West 49th Street. His first job was to go out and solicit business. This he did by the laborious but effective method of just going from office to office in the business sections with a pack of samples in his hand, getting any orders he could, small or large. In the course of these perambulations he reached the old Academy of Medicine building on West 43rd Street. The story runs that when he told the person at the entrance desk the purpose of his visit, he was told to sit down in the corridor. After an interminable wait, a tall, dignified and rather impressive gentleman entered the front door, and, passing by, asked the young man if there was anything he could do for him. The gentleman was Dr. Linsly R. Williams, the first full-time Director of the Academy and the day was his first on his new job. The result of the meeting of these two men was a small order for the printing of some cards. Thus began an association between the young man and the Academy which has endured for thirty-three years.

In 1926, he undertook the publication of what everyone knows as the "Grey Folder," which has become almost an institution in itself and has grown with the years from an eight page pamphlet to its present size of twenty-four pages. Up to 1928, the Academy *Bulletin* had been published by an out-of-town firm and difficulties had arisen in connection with deadlines, publication dates and the problems of mail communication. So in 1928 our energetic young man took over the publication of the *Bulletin*. The *Bulletin* of that period was a modest production,

* Presented at the Annual Meeting of The New York Academy of Medicine, January 2, 1958.

CHARLES C. MORCHAND

drab in format and not too enlivening between its covers. It was in great part a house organ. In 1937, the Editorial Board decided on drastic changes. In these deliberations, our young man played an important role, displaying not only a rare knowledge of the intricacies of type, paper and printing, but as well that rarer quality, an artistic sense. Thus, in 1938, came into being the present format of the Academy *Bulletin* of which we all are proud. There has been no change in this format in twenty years and I hope there will be no change for many years to come. It is known and recognized, not only in this country but also abroad, as an example of the printer's art at its best. In addition to the production of the Grey Folder and the *Bulletin*, our friend has acted as advertising manager, an onerous, taxing and oft-times unpleasant task.

But, more important than the mere recital of facts and dates, has been the spirit of friendly cooperation and help, day in and day out, over thirty-three years that has characterized the association of the Academy with Mr. Charles C. Morchand. No task has been too great or too small. Every problem has been met with vigorous energy, high competence, and a cheerfulness that has endeared him to every member of the Academy staff. As the years have gone on, the relationship of the Academy to Charles C. Morchand has been not merely a business one, or that of publisher to client, but much rather, one of friendship, confidence and trust. He has become a real part of the Academy. Such relationships are rare, indeed.

It was of tremendous personal satisfaction to me as Director and to the members of the staff of the Academy when the Committee, under the Chairmanship of Dr. Cornelius P. Rhoads, charged with the award of this Plaque, given for outstanding service to The New York Academy of Medicine, chose Mr. Charles C. Morchand as its recipient for 1958. I, therefore, have the honor and real pleasure to present this Academy Plaque, on which is inscribed:

PRESENTED TO

CHARLES C. MORCHAND

IN RECOGNITION OF

OUTSTANDING SERVICE TO

THE NEW YORK ACADEMY OF MEDICINE

January 2, 1958

MEDICAL ASPECTS OF CIRRHOSIS OF THE LIVER*

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Cornell University Medical College, New York, N.Y.

GENERAL

PRESENT PICTURE: In terms of treatment, the patient with Laennec's cirrhosis has stimulated new interest in the past 15 years or so. This is because, with a better understanding of the disease, especially of some of the nutritional deficiencies responsible, treatment has assumed a more solid footing and has met with better results. Furthermore, methods, both medical and surgical, have been developed which may successfully handle the major complications which befall the cirrhotic patient, namely, *hemorrhage, ascites* and *coma.* Consequently a patient with cirrhosis today has a somewhat brighter outlook than ever before.

General Treatment: I think it is desirable that, from the beginning if possible, the intelligent patient with cirrhosis be as thoroughly informed as possible about all aspects of his disease. He should be made to realize that he should turn to his physician for advice or treatment of relatively minor medical matters. Thus, for example, fever, due to a neglected upper respiratory infection, may cause an unnecessary esophageal hemorrhage. A tooth extraction that might have been postponed may precipitate unnecessary hemorrhage.

Also, since proper nutrition is the basic treatment of Laennec's cirrhosis, it is well for the patient to understand how the combination of protein deficiency and alcoholic excess causes cirrhosis to develop. Thereby he can better appreciate the fact that the dietary program prescribed has specific therapeutic implications.

It is well for him to be made thoroughly aware of the complications, such as hemorrhage, that will inevitably occur, if the process is not arrested. Such knowledge may serve as a deterrent to further

* Presented at a combined meeting of the Sections on Medicine and Surgery with the Stated Meeting of The New York Academy of Medicine, April 14, 1957 as part of a Symposium on *Diseases of the Liver.* Manuscript received April 1957.

drinking, but, of more importance, it will bring to light esophageal bleeding at an earlier stage, e.g., when only a little melena is present, rather than when a profuse hematemesis occurs.

Dietary Treatment: With regard to diet, the aim in treatment is essentially to correct the protein deficiency that led to the development of cirrhosis. Since deficient protein can cause cirrhosis and excessive protein can cause hepatic coma the amount of dietary protein to be prescribed for a patient with cirrhosis has become a subject of considerable practical interest. While there is wide individual variation, most patients who develop Laennec's cirrhosis have a dietary protein intake averaging less than 20 grams per day, often in conjunction with a high caloric intake usually derived from alcohol. The beer drinker, who consumes all his calories in the form of 8-10 quarts of beer daily, gets about 20 grams of protein in this amount of beer. Although other factors in beer may be responsible, possibly this amount of protein is the factor that accounts for the relative infrequency of cirrhosis in pure beer drinkers, as compared with those who consume an equal amount of calories and alcohol in the form of whiskey or wine which contains no protein.

A similar estimate of the amount of protein required to protect the liver was arrived at in the fascinating world-wide studies on the nutritional disease of children called kwashiorkor, in which acute hepatic disease, somewhat like acute fatty liver, occurs in areas of the world where the diet is deficient in protein despite being adequate in calories. Kwashiorkor occurs in countries where calories derived from protein account for less than about 3 per cent of the total caloric intake. This is equivalent to about 20 grams of protein in a 3000 calorie diet.

Obviously then, the cirrhotic patient needs over 20 grams of protein daily, but just how much more is a question. In nitrogen balance studies on cirrhotic patients ingesting increasing amounts of protein, one finds evidence of comparable increasing utilization of protein until the diet contains about 80 grams of protein daily. Beyond this point, relatively little increase in protein utilization occurs. Hence in general one would aim at at least 80 grams of protein daily. There doesn't appear to be any clear indication that, in conjunction with adequate calories, a protein intake in excess of this gives any additional benefit, and, to be sure, a good clinical response can occur with protein intake considerably below 80 grams a day. However, generally we aim at a bit higher protein intake, e.g., 100-130 grams a day, because it may

be that certain requirements of the damaged liver are better met by higher intakes of protein, such as appears to be the case in recovery from viral hepatitis, where a 3000 calorie diet with 140 grams of protein appeared in one study to effect a more rapid recovery than a similar caloric intake with but 80 grams of protein.

The chief reason for dwelling on this point of the desirable amount of protein to prescribe for a patient with cirrhosis is that an unwarranted fear has arisen that protein is harmful to the usual cirrhotic patient. It is certainly true that dietary protein must be restricted in those cirrhotic patients who manifest ammonia toxicity as a reflection of a decreased capacity to handle large amounts of dietary protein. This problem will be discussed by Dr. McDermott. However, it is important to emphasize that, in general, the need to restrict dietary protein applies to relatively few patients with cirrhosis, and dietary protein should not be restricted except where specifically indicated.

Problems: The patient with cirrhosis faces three major complications, namely, hemorrhage, ascites, and coma, and it is in dealing with various aspects of these that many of the complex problems in medical management arise.

Hemorrhage stands out as the major threat to the life of a patient with hepatic cirrhosis. Every patient with Laennec's cirrhosis should be considered a potential candidate for esophageal hemorrhage. The routine use of esophagrams can provide warning evidence of the presence and the size of esophageal varices. In order to facilitate early treatment of hemorrhage, the patient should be advised about the early signs of esophageal bleeding. It is well for both the patient and the physician to be mindful of the fact that certain things may cause hemorrhage, e.g., fever, especially if prolonged. Also occasionally the expansion of the blood volume following administration of excessive amounts of plasma or albumin may likewise cause esophageal hemorrhage. The routine laboratory tests of hepatic function do not give us any specific warning of impending hemorrhage but they are important to have on file, because if hemorrhage does occur, they may be most useful in helping to evaluate whether any surgical procedure might be considered.

Once hemorrhage occurs one is immediately committed to a course of action that includes first, treatment of the acute stage and secondly, correction of the underlying portal hypertension, if this is feasible.

In the acute stage, prompt blood replacement is important, because

in addition to the usual hazards of hemorrhage, the cirrhotic liver reacts badly to acute deficiencies in circulation such as occur in shock, so that even if hemorrhage is controlled, further hepatic decompensation may rapidly occur as indicated by increasing jaundice and perhaps coma.

Tamponade: When to use esophageal tamponade with the Sengstaken-Blakemore balloon is a problem which must be faced in each patient individually. When a hemorrhage is obviously small, or when the patient has had a single hematemesis and appears to be doing well on blood replacement, the use of the balloon may usually be safely delayed. If major hemorrhage recurs, then there appears to be little reason to delay further. The reason for hesitating at all in the use of the balloon is that while the balloon is generally helpful in controlling hemorrhage, it may in turn cause serious complications. Once the balloon is introduced in the conventional way, there is usually adequate control of the hemorrhage, at least temporarily. Often, however, hemorrhage recurs either as soon as the pressures are reduced, or within a day or two thereafter, so that the pressures must again be raised. This procedure may be repeated once or twice. If control of the hemorrhage with the esophageal balloon is successful the patient should then be prepared for portacaval shunt as soon as he is well stabilized, preferably within a few weeks while he is still hospitalized. If, however, hemorrhage is not controlled with the balloon, or if pressure on the gastric or the esophageal balloon required for control is excessive, a surgical attack under these emergency conditions is justified, if the patient is not obviously an impossible surgical risk. Various surgical procedures are used at this stage. Our preference is the portacaval shunt since thereby, without much more risk than with other available procedures, the reduction in portal pressure and control of hemorrhage can be accomplished in one step. Since whatever surgical procedure used is a major one, the evaluation of surgical risk is difficult. Laboratory tests both pre-hemorrhage and during the hemorrhagic period may be useful but are usually quite distorted and often meaningless and misleading once hemorrhage has occurred. Consequently we often find little to rely on except a general clinical evaluation of the patient's condition. I am sure Dr. Welch will discuss some of these points much more fully.

Ascites: Thus far, in considering factors that guide us in the evaluation of surgical risk, I have not mentioned ascites as a contraindication

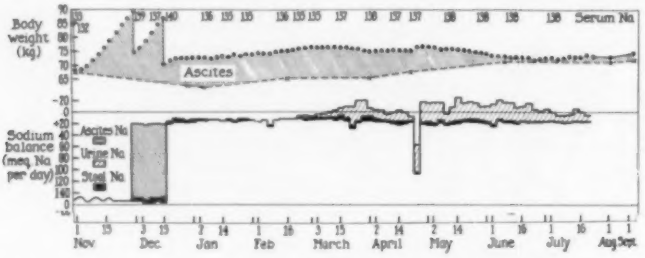

Figure 1—From "Electrolyte Studies on Patients with Cirrhosis of the Liver", W. J. Eisenmenger and associates, The Journal of Clinical Investigation, *29*:1491-99, 1950. Reprinted by permission.

to surgery. For some years it was considered to be a strong contraindication to any major surgery, especially a portacaval shunt. But before discussing ascites from this viewpoint, it would be well to discuss ascites briefly as one of the major complications, arising in the cirrhotic patient, which can be greatly helped by medical management.

The patient with Laennec's cirrhosis may have ascites of varying severity. One may see it come and go within a period of one or two months, in a patient who has mild cirrhosis with superimposed fatty infiltration. As the fat reabsorbs, the ascites disappears. One frequently sees transient ascites in patients with cirrhosis after a hemorrhage, probably reflecting the increased hypoalbuminemia and some temporary deterioration of hepatic function following hemorrhage. One frequently sees patients with cirrhosis with a moderate tendency to form ascites in whom, for several years, there is a small amount of ascites ranging from a trace to several liters, despite no great care in restricting salt. These patients generally respond well to any type of treatment including careful salt restriction, mercurials, calcium chloride, and occasionally Diamox. As hepatic function improves, ascites often disappears.

The major problem, however, exists in those patients, who, on an average intake of about 10 grams of salt a day, gain one liter of ascites daily, who show virtually no response to diuretics, and who require a paracentesis every two weeks or so. This type of patient we should discuss briefly.

For the purpose of control of ascites, we can consider ascitic fluid simply as a solution of salt and water, with a concentration of sodium

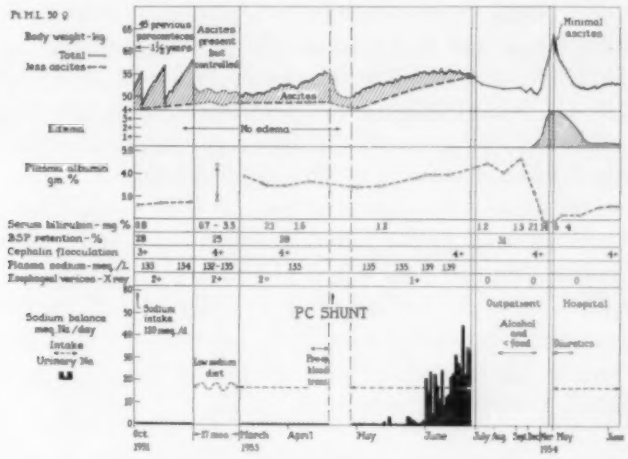

Figure 2—Reprinted from "Relationship of Portal Hypertension to Ascites in Laennec's Cirrhosis", W. J. Eisenmenger and W. F. Nickel, Jr., American Journal of Medicine, June 1956, pp. 879-89. Reprinted by permission.

almost identical with that of plasma. Consequently every liter of ascites contains close to 140 meq. of sodium which is equivalent to 8 grams of NaCl. Hence, for every liter of ascites that accumulates the patient must have ingested at least 8 or 9 grams of salt. The only possible exception is when serum sodium levels are decreasing over short periods of time. In this type of patient with maximal ascites formation, there is virtually no urinary excretion of sodium, and the volume of ascites formed closely parallels the sodium ingested (Fig. 1).

This may all seem elementary, but it is extremely common that this basic fact is overlooked when treating a patient with refractory ascites because one often hears the statement that the patient continued to gain ascites at the rate of 1 liter per day, despite a 1 gram salt diet.

What can we expect in a patient with refractory ascites by using carefully controlled salt restriction? Usually we can expect prompt control of ascites—not disappearance, but control in that the gain of one liter of ascites daily should cease. If it doesn't, serum sodium will rapidly fall, but fortunately this is unusual.

Partly because of our interest in the possible relationship of ascites to portal hypertension in the intra- and extrahepatic portal system, and

partly to determine whether the presence of refractory ascites was necessarily a strong contraindication to a portacaval shunt, five successive patients, who had ascites constantly present for from one to six years, were subjected to end to side portacaval shunts. These were performed by Dr. Nickel (Fig. 2). In each instance the ascites disappeared shortly after the operation and did not recur even if the basic hepatic condition further deteriorated. The disappearance of ascites would appear to be due to a decrease in pressure in both the extrahepatic and intrahepatic segments of the portal venous system, since pressures in both segments were markedly reduced by the end to side shunt.

We don't generally advocate this procedure for the treatment of ascites but in certain selected cases it may be indicated. However, when hemorrhage occurs in a patient with ascites, the ascites *per se* need not be a contraindication to a portacaval shunt.

Summary

In summary I have tried to review some of the pertinent medical problems that face the physician in caring for a patient with Laennec's cirrhosis. Often the major problem is for both the patient and the physician to maintain some degree of optimism, because if the patient tries to get well long enough a surprising number of them will respond. We are all most impressed with the tremendous strides that surgeons have made so that patients who were formerly doomed to die of esophageal hemorrhage or who were excessively burdened with ascites may now be clinically cured. We are all looking forward to hearing more about these problems from Dr. Stuart Welch who has done so much in this field.

It will also be a pleasure to hear Dr. McDermott discuss some of the peculiarities in the cirrhotic patient that permit him to develop ammonia toxicity, accounting for at least some cases of hepatic coma.

THE TREATMENT OF ASCITES BY SIDE TO SIDE PORTACAVAL SHUNT*

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and

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Several attempts have been made to treat ascites by surgical procedures but little success has been attained. Time does not permit a review of this history. It is important to point out, however, that there has been rather unusual agreement that portacaval shunts are of little value in the treatment of ascites and, indeed, they have been considered by some to be contraindicated. This opinion is based on the consideration that portal hypertension, *per se*, is not the cause of ascites and, therefore, splanchnic decompression of the portal system would have little effect on ascites. Clinical observations have largely borne out this contention. It should be mentioned in this regard that portacaval anastomosis is usually performed by the end to side technique in which case the portal vein is severed near the liver, its hepatic end tied and the splanchnic end anastomosed to the vena cava. This operation effectively decompresses the peripheral portal system but should have little effect upon reducing ascites if hypertension is not the cause of ascites.

A review of the mechanisms which may be involved in the production of ascites in hepatic cirrhosis leaves us with the impression that there are four possible causes. These are: 1) inflow block (portal hypertension), 2) decreased oncotic pressure of the blood associated with a low value for serum albumin; 3) retention of water and sodium associated with abnormalities of hormonal systems; and 4) outflow block (obstruction to the egress of blood from the liver). Originally, it was

* Presented by Dr. C. S. Welch at a combined meeting of the Sections on Medicine and Surgery with the Stated Meeting of The New York Academy of Medicine, April 14, 1957, as part of a Symposium on *Diseases of the Liver*. Manuscript received April 1957.
From the Departments of Surgery and Medicine of the Albany Medical College and Albany Hospital, Albany, N. Y. This work was aided by a grant from the United States Public Health Service.

assumed that ascitic fluid arose from the splanchnic bed by transudation, the local mechanical derangement being a combination of portal hypertension and decreased osmotic pressure of the blood. This etiology is not tenable in view of certain known facts, namely, that high degrees of portal hypertension can exist without ascites in patients with cirrhosis of the liver and also with extrahepatic obstructive portal lesions. Also, there is no constant correlation between the blood colloidal osmotic pressure and the rate and volume of peritoneal fluid accumulation. The abnormalities noted in salt and water metabolism and in certain hormonal systems serve to give further information about the general metabolic effects of cirrhosis of the liver but do little to explain the localization of fluid in the peritoneal cavity. Ascites is a local phenomenon and a local mechanical derangement must be present to account for it. The more recent concept of outflow block postulates that there is a mechanical obstruction to the egress of blood from the liver, a diminution in normal efferent flow through the hepatic veins, the local mechanical derangement being a postsinusoidal block leading to venous congestion of the liver. McIndoe[1] showed by injection studies that in cirrhosis of the liver there is a decrease in both the portal venous system and the hepatic venous system within the liver. More recently, Madden, Lore, Gerold and Ravid[2] have demonstrated by injection studies of the hepatic vasculature that in cirrhosis of the liver associated with ascites there is an absolute decrease in the intrahepatic venous system. This relatively greater decrease in the hepatic venous system is not seen in cirrhotic livers taken from patients who did not have ascites. Kelty, Baggenstoss and Butt[3] have demonstrated that the regenerated hepatic lobule is another important cause of obstruction of the hepatic venous system. These observations are very important in establishing the fact of outflow block.

Experimental studies also support the concept that outflow block is the primary cause of ascites and that ascitic fluid is hepatic lymph. It is known that ascites can be produced consistently in dogs by constricting the vena cava above the diaphragm. The ascites which follows this procedure often is not associated with hypoproteinemia or marked elevations of the portal pressure in the initial stages. Clinically, the association of ascites with constrictive pericarditis and the Budd-Chiari syndrome indicates that the obstruction to the venous outflow does not necessarily have to be intrahepatic but may be anywhere between the termination

of the portal system and the right side of the heart. The actual origin of the fluid is probably sinusoidal where obstruction and venous congestion of the liver promote a high filtration pressure with the excessive formation of hepatic lymph which extravasates into the peritoneal cavity. Grindlay, Flock and Bollman[4] have reported on the dilatation of lymphatics in the porta hepatis and measured the markedly increased lymph flow pressure in dogs made ascitic by constriction of the vena cava. Hyatt and Smith[5] have shown the close relationship between the protein content of ascitic fluid and hepatic lymph in dogs with ascites. Many surgeons have noted the outpouring of fluid associated with dissection around the porta hepatis on patients undergoing portacaval shunt operations. This phenomenon is seen especially after the portal vein has been interrupted and during the time of performing the anastomosis, an important finding supporting the concept of outflow block. Mallet-Guy, Devic, Feroldi and Desjacques[6] in France have produced hydrothorax in dogs by constricting the supradiaphragmatic portion of the inferior vena cava and placing one lobe of the liver in the pleural cavity above the diaphragm. This work further supports the belief that ascites is hepatic lymph. The actual route of the intrahepatic lymph flow has not been completely determined. However, available data support the theory that consequent to congestion of the liver, there is engorgement of the subcapsular lymphatics and the lymphatics of the porta hepatis with extravasation of lymph from engorged lymphatics into the peritoneal cavity.

Our observations support the concept of outflow block as the basic mechanical factor in causing ascites. Aside from paracentesis and operations designed to drain ascites from the peritoneal cavity (unsuccessful to date) there are two rational approaches to the surgical treatment of ascites: 1) Reduction of hepatic inflow or 2) the production of additional outflow. Rienhoff and Woods[7] in 1953 proposed that ligation of the hepatic artery should be beneficial in the treatment of ascites. Assuming that ascites is secondary to hepatic venous obstruction, reduction in the afferent flow would serve to decompress the liver. Hepatic artery ligation has been given a trial but has not been accepted as a sound procedure because the consequences of arterial ligation negate the beneficial effects upon the ascites. Others have sought to reduce ascites by diverting the portal inflow. Eck originally devised his fistula as a means of treating ascites. Eisenmenger and Nickel[8] in 1956 reported

five cases in which ascites was present and in which end to side portacaval shunt had been done with apparent beneficial effect upon the ascites. This experience has not been universal and most surgeons have rejected the idea of portacaval shunt as having a predictable effect upon ascites. Nature, however, has provided a means by which it is possible to divert portal inflow and, simultaneously, a portion of the arterial inflow without incurring the disadvantages of total arterial occlusion. Two types of intrahepatic arterial portal anastomoses exist, arterioportal, which lie within the portal space, and arteriosinusoidal, which lie outside the portal space. Herrick[9] showed in 1907 that in cirrhosis of the liver the communications between the arterial bed and the portal system increased with the development of new abnormal arterioportal venous anastomosis. In cirrhotic livers, he showed that portal pressure rose markedly as hepatic arterial pressure was increased. He also showed that when the hepatic artery was perfused, there was a free flow through both hepatic and portal veins. In the normal liver, the portal return-flow was less in volume than from the hepatic vein. In the markedly portal cirrhotic liver, the portal return-flow was always greater than from the hepatic vein. We have found that upon occluding the portal vein in patients with ascites and measuring the portal pressure on the liver side of the occluding clamp, the recorded pressure will often be surprisingly high. In several of our cases, it has been over 250 mm. of water.

These findings suggest that the portal vein can act as a decompressive outflow route in certain circumstances. It occurred to us that if we could arrange to decompress the liver, using the portal vein as an exit for the excess of blood trapped within the liver, we might affect the formation of ascites. In an end to side portacaval shunt the distal end of the portal vein is ligated. However, in a side to side portacaval shunt the portal vein is left in continuity and both the splanchnic end and the hepatic end are allowed to drain into the low pressure caval system. Thus, a portion of the hepatic artery blood can drain into the vena cava via the natural intrahepatic arterial-portal and the artificially created portacaval anastomoses. The inflow to the congested liver would be further decreased by that amount of portal blood from the splanchnic bed which would be diverted into the vena cava by the same side to side portacaval anastomosis.

We, therefore, have performed side to side portacaval shunt in six

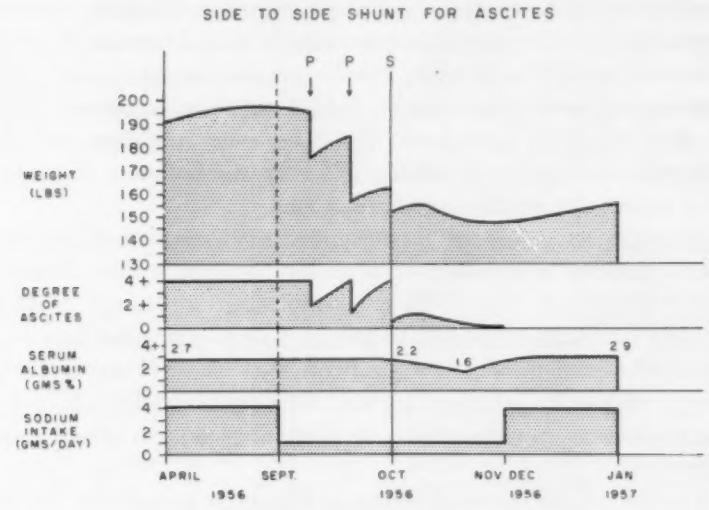

Figure 1.

Graphic representation of control of ascites after side to side portacaval shunt in a 47 year old male patient with alcoholic cirrhosis of the liver. P., paracentesis. S., portacaval shunt. Note the absence of ascites after portacaval shunt in the presence of very low serum albumin values. Also, the resumption of an intake of sodium chloride of over 4 grams did not cause re-accumulation of ascitic fluid.

patients with intractable ascites. In each case, the ascites has been relieved, although the follow-up has been short (eight months to two months). One patient was inadvertently given large doses of ammonium chloride at home for the treatment of leg edema and succumbed from ammonia intoxication. The others have done well. Their ascites has not re-accumulated and their liver function has improved. This group of patients had poorer liver function than patients usually subjected to portacaval shunt for the relief of hypertension and prevention of bleeding. Figure 1 graphically represents the course of one patient subjected to side to side shunt for ascites. It was particularly noteworthy that ascites did not re-accumulate even though the values for serum albumin were very low in the postoperative period (Figure 1). Of considerable significance is the fact that the five surviving patients have resumed a normal salt intake without precipitating a recurrence of ascites.

This communication is a preliminary report on a short-term follow-up of side to side portacaval shunt in the treatment of ascites, presented because the clinical results seem convincing to us and because the rationale seems adequate for a trial of this operation on other cases. Additional clinical investigation can be carried out on these patients before and after the shunt procedures. We have some indication that their ability to excrete sodium is considerably enhanced but more documentation is needed for establishing this as a fact.

Ascites is, of course, to be controlled by medical measures in all patients. Careful management can usually accomplish this. There are cases of intractable ascites which usually manifest themselves after a month or six weeks of medical treatment. Side to side shunt may be an adjunct to the treatment of such patients in the light of our recent experience with it. It also should prevent bleeding from varices if they be present since it simultaneously decompresses the peripheral portal system.

A review of the literature on side to side shunt reveals that although no one has recommended this procedure for the treatment of ascites alone, a few instances of relief of ascites have followed the procedure. Large, Johnston, and Preshaw[10] report three cases of ascites in which side to side shunt was performed with some amelioration of the ascites. Theron and Allan[11] used an "H" shunt, in which a vein graft is employed between the portal vein and vena cava, in five patients with portal hypertension and bleeding. Two of these patients had ascites and were relieved. Again, however, these authors did not recommend the operation for ascites alone although the "H" graft technique was designed by them to decompress the liver, a rationale similar to ours.

Some investigators state that a portacaval shunt has the disadvantage of depriving the liver of blood. However, it is well known that in many cases of cirrhosis with well developed collateral circulation, much of the portal blood is shunted around the liver. In cirrhosis with ascites, the added factor of outflow block is present and there is evidence that in certain of these cases the flow in the terminal part of the portal vein system may actually be retrograde, depending on the degree of outflow block and arterial mixing. In regard to depriving the liver of arterial blood by such a shunt, it can be said that the actual amount of blood needed by the liver is not known. It is agreed, however, that congestion of the liver is not beneficial. The amount of arterial deprivation af-

forded by this operation is difficult to determine because of the nature of the intrahepatic anastomoses but the amount of retrograde flow is dependent on the degree of outflow block and is to a great extent a self-regulating mechanism. Side to side shunt, therefore, offers a means of decompressing the liver which imitates nature. It shows promise in the treatment of ascites.

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AN ENDOCRINE PROBLEM

*Transcription of a Clinical-Pathological Conference**

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PROTOCOL

THE patient was a 52-year-old white female executive who had been under observation during four years preceding her death. While waiting in the receiving room for her third admission to the hospital she suddenly stated "I can't breathe," became cyanotic, pressed her chest, and expired.

She was first seen while ambulatory at age 48. At this time she stated that occasionally during the preceding year she had had sharp pains in her left chest which lasted 2-4 minutes and were accompanied by shortness of breath and apprehension. She had not had orthopnea or ankle edema or any other complaints. Her menopause had begun at age 35 and her last menstrual period had occurred at age 41. Initial physical examination was negative except for a blood pressure in both arms of 160/100. The electrocardiogram was entirely normal in the standard, chest, and unipolar leads; the orthodiagram was also normal. The patient was told that she did not have any signs of active heart disease. She was given phenobarbital

* Presented at the Twenty-Ninth Graduate Fortnight of The New York Academy of Medicine, October 24, 1956.

which diminished her nervousness. Her blood pressure three months after the initial examination was 140/90 and 12 months afterwards was 160/95.

Seventeen months after initial observation, the patient had a severe precordial pain which lasted for 40 minutes and extended to the left biceps as well as to the tongue; this was accompanied by acute shortness of breath. The following day she had another attack of severe precordial pain which again lasted for some 40 minutes and extended to both shoulders and down to both elbows. A third attack occurred on the succeeding day and persisted all night. When the patient was seen at this time she was quite apprehensive, tense and agitated. The blood pressure was 170/120 in the right arm and 165/150* in the left. The PMI was 2 cm. beyond the mid-clavicular line. There was no pulmonary edema and the liver was not enlarged. The fundi showed Grade 2 retinopathy. The electrocardiogram showed left axis deviation and inversion of the T waves in all the chest leads and also inversion in AVL. A presumptive diagnosis of acute myocardial infarction was made and the patient was hospitalized. She remained in the hospital for five weeks during which time evolutionary changes in successive electrocardiograms suggested anterior myocardial infarction. She was maintained on anticoagulant therapy. The sedimentation rate by the Wintrobe technique was 34 on admission and 16 at the time of discharge. She had a persistent 1 plus albuminuria. Her blood pressure never deviated substantially from 160/110.

During the last week of her first hospitalization and up until her second hospital admission six months later the patient was maintained on Rauwolfia serpentina, nitroglycerin, and chloral hydrate. Her blood pressure ranged between 160/110 and 190/115. She occasionally expressed concern because she was losing hair from her scalp and growing hair on her face and chest, and because her skin was greasy and she was developing acne. It was noted that her body had a male configuration and that her breasts were small. Some five months following discharge from the hospital she developed left ventricular failure, which was characterized by engorged neck veins, bilateral basal rales, engorged liver and peripheral edema. She was digitalized and given Mercuhydrin, and for about a month refused hospitalization, but was then readmitted because of persistent edema and increasing weakness.

On her second admission to the hospital the patient's blood pressure was 180/100. She was plethoric and the liver was down 7cm. in the mid-clavicular line. Digitalis and mercurial therapy were given because of peripheral and pulmonary edema. She had an acne-form rash over the chest and back. There was some increase in hair on the face and moderate alopecia, particularly in the temporal regions. At this time, fleshiness of the trunk was noted, but the extremities seemed unremarkable.

Laboratory Data (2nd Admission):

Urine: Sp. Gravity 1.022; 1 plus albuminuria; 2 plus sugar; 80-100 white cells per HPF. Blood: Hgb. 15.5 gms.; red count 5.1 million; hematocrit 48. White count 11,900 with a normal differential. Sedimentation Rate 13. Carbon dioxide combining power 34 m.mols.; chlorides 92 m.eq./L, sodium 131 m.eq./L, potassium 4.7 m.eq., calcium 9.6 mg., phosphorus 3.2 mg. Glucose tolerance curve: Fasting blood 103, ½ hour 187, 1 hour 277, 2nd hour 350, 3rd hour 239. Serial

* Should read 165/115, see pp. 260, 261, 274 in text.

electrocardiograms revealed evolution toward normal such as seen after an anterior myocardial infarction. X-ray studies of the chest revealed multiple soft, round densities 0.5 to 1.5 cms. across throughout the left lung field. Heart was slightly enlarged. Skull x-rays revealed demineralization of the dorsum sellae and the clinoid processes; the sella turcica was normal in size. Complete skeletal survey revealed evidence of diffuse osteoporosis but no sign of osseous metastases. Nephrotomograms revealed that the left kidney was displaced laterally by a mass which occupied much of the left upper quadrant. Seventeen ketosteroids excreted during the first 24 hours after admission, 84 mg. (normal 9-11 mg.). Ten days later she excreted 124 mg. of 17 ketosteroids during 24 hours. Blood level of 17 hydroxycorticoids was determined on two occasions. Once this was found to be 48 micrograms per hundred milliliters; after 4 hours of intravenous ACTH the level rose to 62 micrograms per hundred milliliters. On another occasion the 17 hydroxycorticoids were found to be 28 micrograms per hundred milliliters; after 25 mg. of intravenous ACTH, 20 micrograms. Both these tests were interpreted as exhibiting no significant change after intravenous ACTH.

The patient was discharged after two months in the hospital and followed for the next three weeks at home. During this interval she developed pustules all over her body, together with massive peripheral edema, cyanosis and anorexia. While being admitted to the hospital for the third time, she expired as described above.

CHAIRMAN JOHN G. KIDD: Welcome to this Clinical-Pathological Conference of the Twenty-Ninth Annual Graduate Fortnight.

Since we are all in more or less neutral territory here, perhaps it might be well for me to outline briefly what I think our ground rules should be. The first essential of a successful CPC is to have participation of the audience and I hope you will think along with all of us in this exercise and feel free to ask questions by the written form or verbally, as you choose.

With respect to the abstract, I must accept responsibility for all the errors in it, though I have been assisted in compiling it by two very able clinicians, one of whom attended the patient, so that I think most of the information in it is accurate. I have exercised editorial privilege, however, in one respect: namely, I have deleted from the abstract one clinical observation and a pertinent one, which I am prepared to disclose upon direct inquiry but not otherwise. With that preamble and with the additional statement that, so far as I know, none of the distinguished clinicians who have consented to come and give their opin-

ions of this case has any knowledge of the final diagnosis or the anatomical findings, I think we should now proceed to introduce Dr. Claude Forkner of New York Hospital, who will discuss the general medical aspects of this problem.

DR. CLAUDE E. FORKNER: We all know that Dr. Kidd would do something like that to us, leave out the most important point. I shall go through this clinical abstract with you, discuss it point by point from the general medical point of view and leave to these other specialists the more detailed considerations so far as the endocrine problem is concerned.

The patient was a 52 year old white female executive who had been under observation four years preceding her death. While waiting in the receiving room for her third admission to the hospital, she suddenly stated, "I can't breathe", became cyanotic, pressed her chest and expired.

She was first seen while ambulatory at age 48, in other words, four years before death. At this time, at the age of about 47, she stated that occasionally during the preceding year she had had sharp pains in her left chest, which lasted two to four minutes. The duration of the episode of pain is important, I think. These symptoms were accompanied by shortness of breath and apprehension. She had not had orthopnea or ankle edema, or any other complaints. When a patient of this age has pain in the left chest lasting from two to four minutes, accompanied by shortness of breath and apprehension, one's attention is immediately called to the heart and one thinks of coronary artery disease in which insufficient oxygenated blood is going to the myocardium. One has to think also of certain other disorders such as a hiatus hernia. One should think possibly of gallbladder disease but the main thing that one thinks of, especially if the patient dies of the disorder, is coronary artery disease. The protocol does not say whether these pains occurred with effort or not. She had not menstruated for some time. Her menopause had begun at age 35, rather early, and her last menstrual period had occurred at age 41.

The initial physical examination was negative except for an elevated blood pressure in each arm of 160/100. It is customary when obtaining a blood pressure of that type in the arms also to take the blood pressure in the legs, but we have no record of any blood pressure being taken in the legs. Nor have we a statement in this protocol about pulsations in the femoral arteries, in the dorsalis pedis or in the posterior tibial

vessels. The electrocardiogram was entirely normal in the standard and unipolar chest leads. By the way, Dr. Kidd, was the blood pressure taken in the legs?

CHAIRMAN KIDD: That was not the significant observation omitted from the abstract.

DR. FORKNER: The orthodiagram, the electrocardiogram and the size and shape of the heart were considered to be normal. The patient was told that she did not have any signs of heart disease and was given phenobarbital which was said to have lowered the blood pressure. Her blood pressure three months after the initial examination was 140/90 and 12 months afterwards 160/95, a distinct but not marked elevation of blood pressure at every observation.

In other words, 17 months after the initial observation perhaps two to three years before she died, the patient had severe precordial pain which lasted for 40 minutes and radiated to the left biceps as well as to the tongue. This was accompanied by acute shortness of breath. The following day she had another attack of severe precordial pain, which again lasted some 40 minutes and which extended to both shoulders and radiated down both arms to the elbows. That sounds like a real pain of coronary artery insufficiency. A third attack occurred on the succeeding day and persisted all night. We don't know whether these were associated with effort or not, presumably not. When the patient was seen at this time she was quite apprehensive, tense and agitated. The blood pressure was 170/120 in the right arm and then a very remarkable blood pressure 165/150 in the left arm. I think that may be an error, for that gives a pulse pressure of only 15 mm. of mercury. Is that the correct figure, Dr. Kidd?

CHAIRMAN KIDD: So far as I know it is. I will check on the point. If otherwise, I will let you know in a moment.

DR. FORKNER: The point of maximum cardiac impulse was 2 cm. beyond the mid-clavicular line. In other words, the heart had changed, had become enlarged. The blood pressure had gone up and the heart had increased in size. There was no pulmonary edema. The liver was not enlarged. The fundi showed grade II retinopathy. The electrocardiogram showed left axis deviation and inversion of the T waves in all the chest leads. You have a reproduction of the electrocardiogram and can observe the abnormalities. I think one can draw no other conclusions. A presumptive diagnosis of acute myocardial infarction was made, the

patient was hospitalized. She remained in the hospital for five weeks during which time evolutionary changes in successive electrocardiograms suggested that an anterior myocardial infarction had occurred. She was maintained on anticoagulant therapy. The sedimentation rate by the Wintrobe technique was 34 mm. fall in one hour on admission and 16 mm. fall at the time of discharge. In other words, she presumably had some acute manifestation, demonstrated in the electrocardiogram, demonstrated by enlargement of the heart, demonstrated by the increased sedimentation rate and then changes which indicated that that was evolving back towards normal. She had persistent 1 plus albuminuria. The blood pressure never deviated substantially from 160/110.

CHAIRMAN KIDD: Dr. Forkner, I am embarrassed to say that there is an error with regard to the blood pressure of 165/150, which you mentioned. Dr. Koteen is prepared to give us the correct figure now.

DR. HERBERT KOTEEN: 165/115.

DR. FORKNER: That sounds a little better.

During the last week of her first hospitalization and up until the second hospitalization, six months later, the patient was maintained on Rauwolfia, nitroglycerin and chloral hydrate. The blood pressure ranged between 160/110 and 190/115. She occasionally expressed concern because she was losing hair from her scalp and growing hair on the face and chest and because her skin was greasy and she was developing acne. This, of course suggested adrenal cortical hyperfunction. It was noted that her body had a male configuration. Her breasts were small. Some months following discharge from the hospital she developed left ventricular failure, which was characterized by engorged neck veins, bilateral basal rales, engorged liver and peripheral edema. She was digitalized and given Mercuhydrin. For about a month she refused hospitalization, but was then readmitted because of persistent edema and increasing weakness.

We have been told here several times that she was given digitalis. We never have been told whether or not she derived any effect from it.

On the second admission to the hospital the patient's blood pressure was 180/100. She was plethoric and the liver was down 7 cm. below the costal margin in the mid-clavicular line, a really large liver. Digitalis and mercurial therapy were given because of peripheral and pulmonary edema. Whether effective or not we do not know. She had an acneform rash over the back and chest, some increase of hair on the face and

moderate alopecia of the scalp, particularly in the temporal regions. At this time, fleshiness of the trunk was noted, but the extremities seemed unremarkable. The fleshiness of the trunk does not mean very much to me. The protocol might have concealed, avoided something there.

At the time of the second admission the specific gravity of the urine was 1.022 and there was one plus albuminuria. That would be expected with hypertension. The urine also exhibited 2 plus sugar and we find later that she had an elevated glucose tolerance test. That argues strongly for diabetes mellitus. She had from 80 to 100 white blood cells per high power field in the urine, which suggests the presence of urinary tract disease, some infection possibly associated with stones in the kidney, pyelonephritis or cystitis or a combination of these disorders. The hemoglobin was 15.5 gm. per 100 cc. of blood; the red count 5.1 million per cu. mm.; hematocrit 48 per cent, a little higher than normal, suggesting a mild polycythemia. The white count was 11,900 with a normal differential. If this were going to be Cushing's disease we would not expect a normal differential. We would expect perhaps that there would be very few eosinophils, under 50 per cu. mm. We would expect that perhaps she might have a lymphopenia, increase in polymorphonuclear neutrophils. The sedimentation rate is 13, the CO_2 combining power 34 millimols which is a little high. The chlorides were 93, which is low. The sodium 131 which is perhaps a little low; the potassium 4.7 m.eq.; the calcium 9.6 mgm.; phosphorus 3.2; the glucose tolerance curve showed that of a diabetic. Serial electrocardiograms showed evolution toward normal, such as seen after anterior myocardial infarction and that was, you remember, the diagnosis suggested by the electrocardiogram. X-ray studies of the chest revealed multiple soft round densities from one-half to one and one-half cm. across throughout the left lung field.

CHAIRMAN KIDD: Would you like to see an image of this radiogram?

DR. FORKNER: I would indeed! (Film) You will see over there by the left scapula a rounded density, another one at the level of the third anterior rib and the third anterior interspace, and still another one in the region of the first interspace on the left. The heart perhaps is a little enlarged without any unusual configuration. The hilar shadows are normal. There may be some cloudiness in the right upper chest. It looks to me as if there is more cloudiness than normal in the first and second interspaces on the right side suggesting a rather diffuse process in that

right upper lung field and a nodular process in the left lung field. Would you agree with that?

DR. ABBIE I. KNOWLTON: Yes, I would.

DR. FORKNER: In other words, we have here something in addition to what is stated in the protocol. There is evidence of a lesion in the right upper lung field which is not too precise and is diffuse. These nodular densities in the left chest certainly suggest tumor, multiple, nodular, round, well circumscribed densities.

The heart was slightly enlarged. Skull x-rays reveal demineralization of the dorsum sellae and clinoid process. The sella turcica was normal in size. Complete skeletal survey revealed evidence of diffuse osteoporosis but no sign of osseous metastases, and I suppose no fractures of the vertebra. As you know with extensive osteoporosis in Cushing's disease it is not infrequent to have compression fractures. I assume none were present. Nephrotomograms revealed that the left kidney was displaced laterally by a mass which occupied much of the left upper quadrant. When you find a mass in the left upper quadrant the first thing you think of is an enlarged spleen. If a mass displaces the kidney, it is apt to be either connected with the kidney, closely approximating it, or behind the kidney. The spleen does not displace the kidney, so this cannot be spleen but it is presumably a mass in the adrenal region, which has displaced the kidney. The 17-ketosteroids excreted during the first 24 hours after admission amounted to 84 mg. That is distinctly high. Ten days later she excreted 124 mg. of 17-ketosteroid. The blood level of hydrocorticoids was determined on two occasions. Once this was found to be 48 micrograms per hundred milliliters; after 4 hours of intravenous ACTH the level rose to 62 micrograms per hundred milliliters. On another occasion the 17-hydroxycorticoids were found to be 28 micrograms per hundred milliliters; after 25 mg. of intravenous ACTH, 20 micrograms. Both these tests were interpreted as exhibiting no significant change after intravenous ACTH.

I shall leave the interpretation of those studies to Dr. Soffer and Dr. Knowlton. Such values, I believe, represent a pathognomonic sign but we have learned in these conferences that nothing is pathognomonic. All that glitters is not gold. There is nothing more certain to induce humility than a clinical pathological conference.

The patient was discharged after two months in the hospital and followed for the next three weeks at home. During this time she de-

veloped pustules all over her body, together with massive peripheral edema, cyanosis and anorexia. While being admitted to the hospital for the third time, she expired as described in the first paragraph of the clinical abstract.

Now my conclusions from this are that she had coronary artery disease and that she almost surely had an anterior myocardial infarction. She had some disease of the kidney, which is presumably a pyelonephritis. This is based on the finding of 80 to 100 white blood cells in the urine, the story of hypertension, albuminuria, and retinopathy. We must also look for calcium in the kidneys because of the extensive osteoporosis and we should look for infection in the kidneys. The obvious diagnosis that Dr. Kidd wants us to make is Cushing's disease. but we have not heard very much about obesity, one of the characteristics of Cushing's disease. We have heard about hirsutism. She has hypertension. She has gonadal dysfunction. She has osteoporosis. She has diabetes. All of those manifestations favor Cushing's disease but we have none of the skin manifestations that are common in Cushing's disease. We do not have the body configuration that is ordinarily associated with Cushing's disease. We have some of the skin manifestations, the acne, but I am referring to the striae and the thinness of the skin and hemorrhagic manifestations that commonly occur. We have heard nothing about those. In Cushing's disease the muscles are affected. There is usually great weakness. We have heard nothing about that. It is true that in Cushing's disease patients have coronary artery disease rather frequently. They have hypertension and they often have pyelonephritis or renal calculi. There is nothing that is especially characteristic about the blood although the red blood cells, hematocrit and hemoglobin are compatible. If she has Cushing's disease or the adrenogenital syndrome, the question is which. She has one of those two and is it that or is it some other mysterious disease, possibly a tumor of the ovary? I think the mass in the left upper quadrant displacing the kidney is very significant and probably indicates a mass in the adrenal. She died of one of two or three disorders. The first disorder one thinks of is a ruptured heart on the basis of the known myocardial disease. One must think also of a ruptured aorta, particularly if she happened to have low blood pressure in the legs, if she had coarctation of the aorta. Presumably she did not have that. One must think also of a massive pulmonary embolus. It happens with carcinoma involving the adrenal gland. Occasionally that

tumor extends into the renal veins and then into the inferior vena cava and she could have an embolism from the inferior vena cava into the lungs producing sudden death. She could have a massive embolism from other causes. She exhibited swelling in her legs, massive edema. There was no mention of phlebitis or of any inflammation. We were led to believe that the edema was due purely to cardiac insufficiency. So the best I can do is to say that this woman probably has an excess production of adrenal corticosteroids, that the best approach that I can make to this is Cushing's disease and this Cushing's disease is associated with a malignant tumor of the left adrenal, although there are some facts against it. Probably she died of one of three causes, either a rupture of the heart, a rupture of the aorta, or a massive pulmonary embolus. I would predict that her right adrenal would be atrophied.

CHAIRMAN KIDD: Thank you very much, Dr. Forkner. We shall all have the opportunity of questioning Dr. Forkner after we have heard from the two other specialists on the panel.

Dr. Abbie Knowlton has generously come down from Columbia, P. & S., to discuss this case and we shall be particularly eager to have her evaluation of the endocrine status, the possibility of Cushing's syndrome and also her interpretation of the laboratory findings having to do with the excretion of 17-ketosteroids.

DR. KNOWLTON: Dr. Kidd, I have really very little to add to Dr. Forkner's discussion. I should like to take up a few points to be considered in arriving at a diagnosis of Cushing's syndrome in this patient.

I should like to ask Dr. Kidd, if a few of the things he has held out on us come from the physical examination. Did she have striae?

CHAIRMAN KIDD: No.

DR. KNOWLTON: The finding of purple striae would have been very helpful. Although we do not find this abnormality in more than two-thirds of patients with Cushing's syndrome, the fact that it is *not* found in other diseases makes it highly diagnostic. She has mild hirsutism, which is in keeping with Cushing's syndrome. Rarely do these patients have true virilism. She did have central obesity, although not marked; had hypertension and plethora, all compatible with the suggested diagnosis. As far as her laboratory data go, I think that perhaps it is not too disturbing that her hemoglobin and white count are pretty close to the normal range. Certainly an occasional patient shows a very striking increase in red count and white count but in the majority, these

values are normal. She does have several important abnormal laboratory findings that would fit the diagnosis of Cushing's: the disturbed carbohydrate tolerance, the extensive osteoporosis and the elevation of 17-hydroxycorticoids in the blood. As you know, the patient with Cushing's may not have an elevated circulating plasma corticoids on every determination. For this reason I think the normal value of 28 micrograms per 100 ml. does not detract from the diagnostic significance of the impressively elevated level obtained on a repeat determination.

Accepting the diagnosis of hyperadrenalism, I think we can say a few words about the etiology of her Cushing's. As you know, the adrenal abnormalities which may occur in the Cushing's syndrome fall into two large categories; those in which the adrenal is hyperplastic and those in which the adrenal is the site of a neoplasm.

In the group in which the adrenal is hyperplastic there is a very characteristic abnormal and "hyper" response to a four hour ACTH infusion. The normal individual given an infusion of 25 mg. of ACTH will show an increase in the circulating corticoids from initial levels of 3 to 28 micrograms per 100 ml. up to about 35 to 50 micrograms per 100 ml. Values in the patient with Cushing's syndrome and hyperplastic adrenals may initially be normal but will rise to a considerably greater than normal degree by the end of the infusion. No rise occurred in our patient when given ACTH on two separate occasions and I think for this reason it is unlikely that her adrenals were the site of hyperplasia. This being so, I would suspect she had a tumor.

If there is a tumor present, it could, of course, be either benign or malignant. In the group of patients with Cushing's syndrome that Dr. Ragan, Dr. Plotz and I reviewed, malignant tumors occurred more commonly than benign. However, in a series reported by Cope of Boston, the reverse was true. In the patient with tumor the response to ACTH may resemble that of the patient with hyperplastic glands. At other times, and this is when it is most helpful diagnostically, the patient with a tumor may show *no* rise in blood corticoids after ACTH. Therefore on the evidence of her unresponsiveness to ACTH, we can deduce that this patient had an adrenal tumor.

From the response to ACTH, we can not make a differential diagnosis as far as the type of tumor goes. In this regard, however, the excretion of 17-ketosteroids in this case is most helpful. The patient with Cushing's syndrome due to hyperplasia has normal or, at most,

very slightly elevated 17-ketosteroids. The patient with a benign tumor may have a normal or even somewhat reduced excretion of 17-ketosteroids. This patient, who has extraordinarily high levels, fits most logically into the group of malignant tumors, where such values are frequently seen. This would of course be compatible with the information suggesting a mass in the left flank and the possible metastases in the chest.

The lack of response to ACTH makes it unlikely that this patient is an example of that rare case of Cushing's which has a carcinoma of the pancreas and an associated hyperplasia of the adrenals, or a neoplasm of the thymus. In such instances the adrenals have usually been found to be hyperplastic and we would expect them to show the same type of response as the hyperplastic adrenal.

I would like to speculate a little about how many of this woman's symptoms can be ascribed to a tumor of the adrenal. Can we say that any of her myocardial difficulties were the result of her Cushing's disease? Surely the incidence of cardiac disease in patients with Cushing's is very high and in a large series some 30 per cent have died in cardiac failure. We know that increased amounts of adrenal hormones probably do increase the amount of arteriosclerosis present. This point, very hard to establish in the adult, has been documented in pathological studies done in children given steroid therapy by Ethridge and Hoch-Ligetti. Can we explain this woman's myocardial infarction of two years ago? Can we explain the amenorrhea starting at the age of 41? Can we tie it all into what she would seem to have terminally—i.e., an adrenal tumor? I have reviewed the history of a number of patients with malignant tumors of the adrenal and Cushing's syndrome as to the duration of life and I was interested to find that seven out of 19 had symptoms extending over two years and particularly interested to note a Danish report, in which the patient's first symptoms of hyperadrenal function began ten years before her death from carcinoma of the adrenal, with metastases. So I think that it is possible that the symptoms in our patient today could all be related to her adrenal tumor, although I am sure we could never prove the point.

There is only one other thing that I should like to mention apropos of the demineralization of the sella. I think it is probably just part of the general osteoporosis and that since the pituitary is not enlarged and the sella outline still visible, this finding does not imply that a

pituitary tumor is present. We would expect to find, of course, histological evidence of pituitary abnormality, i.e., degeneration in the basophils of the pituitary.

DR. FORKNER: May she not have had an adenoma in the pituitary without any demonstrable change in the sella?

DR. KNOWLTON: Yes indeed. Basophilic cell tumors do not ordinarily increase the size of the pituitary.

CHAIRMAN KIDD: Dr. Louis Soffer has also consented to give us his evaluation. We will now hear from him.

DR. LOUIS J. SOFFER: For the reasons that you have heard so well expressed, we would agree that this woman has adrenal cortical hyperfunction. When one speaks of adrenal cortical hyperfunction, as I have had occasion to emphasize so often, it is important to bear in mind the existence of two different sets of signs and symptoms,—those concerned with changes in sex and those concerned with metabolic abnormalities. The term "Cushing's syndrome" actually applies to the metabolic abnormalities such as the hypertension, the disturbance in carbohydrate metabolism, the osteoporosis, plethora, etc.

Most patients with adrenal cortical hyperfunction have a combination of both types of clinical manifestations. There are patients who have pure virilism and patients who have pure Cushing's syndrome, but by and large, the patients who have Cushing's syndrome also show, in varying degrees, minor evidence of virilism.

In our series of some fifty-odd patients with Cushing's syndrome whom we have observed in our clinic over the past 15 years, approximately a third had very modest evidences of virilism and another third had somewhat more virilism. The combination therefore is by no means unusual. The degree of virilism in combination with Cushing's syndrome is of some clinical moment. The fact is that when a patient has Cushing's syndrome and in addition a considerable amount of virilism, the presence of an adrenal cortical tumor is strongly suggested although this is not invariably so. Nevertheless, it occurs with sufficient regularity to make this point of some clinical significance. The patient under discussion today certainly has evidences of Cushing's syndrome, but in addition she presented an acneform eruption, oily skin, male configuration, small breasts and hirsutism. These are all evidences of virilism and virilism of a considerable degree, so much so that on the basis of the story alone one could reasonably suspect

the presence of an adrenal cortical carcinoma.

For reasons which Dr. Knowlton has already described, I think we can be sure that this is so. She has a very considerable increase in the urinary excretion of the neutral 17-ketosteroids. It is important to bear in mind that in patients with Cushing's syndrome it is unusual to find a considerable increase in the urinary excretion of these fractions except in the presence of adrenal cortical carcinoma. In benign tumors there is often a reduction. In adrenal cortical hyperplasia there is generally a modest increase. Therefore the presence of Cushing's syndrome in association with a considerable amount of virilism, with a marked increase in the daily urinary excretion of the neutral 17-ketosteroids, strongly suggests the presence of a carcinoma of the adrenal cortex.

In our experience in carcinoma of the adrenal cortex there has almost always occurred a very considerable elevation of the plasma 17-hydroxycorticoids. Following the administration of ACTH to such patients there usually occurs no further increase of the plasma corticoids. However, we have encountered one instance of a patient with Cushing's syndrome with proven carcinoma of the adrenal cortex, in whom there occurred a very considerable increase in the plasma 17-OH-corticoids following the administration of ACTH.

In any event, the point to emphasize is that the interpretation of this test is dependent not upon whether there is a positive response but on the absence of a response. The absence of an increase in the plasma 17-hydroxycorticoids following the administration of ACTH is strongly in favor of tumor, although it does not necessarily help in distinguishing between a benign and malignant tumor. The presence of an adequate response may occur either in the presence of hyperplasia or benign tumor and occasionally in the presence of a malignant one. Therefore, since she had a very considerable increase in the urinary 17-ketosteroids, a fair amount of virilism as well as the evidence of Cushing's syndrome and since adequate response in the plasma 17-hydroxycorticoid following the administration of ACTH did not occur the probabilities are that she had a malignant adrenal cortical tumor. This is supported by the clinical observation that she had a mass in the left upper quadrant of the abdomen and an area in the left lung field, strongly suspicious of a metastatic lesion.

The story of this patient is an interesting one. She was a 52 year old white female executive, who had been under observation during

the four years preceding her death and it is only six months prior to her death that we begin to hear anything about the presence of virilism. She has had hypertension for at least four years and for a five year period she has obviously had coronary artery disease. A year before admission she began to have pain in the left chest. The pain is suggestive of coronary artery disease since it is associated with anxiety and some shortness of breath. If we have any doubts as to whether this constituted an anginal syndrome, the fact remains that a year and a half later she had what appeared to be a myocardial insult. We can be certain therefore that she had coronary artery disease. However, it is only three and a half years later that the clinical picture of Cushing's syndrome and virilism began to unfold. It is possible, as Dr. Knowlton has said, that the first manifestation of adrenal cortical hyperfunction may be hypertension and coronary artery disease.

You probably know that in adrenal cortical hyperfunction, either spontaneously or exogenously induced, there occurs a considerable hypercholesterolemia, and the concomitant presence of extensive arteriosclerotic changes. One is therefore, not astonished by the fact that she had evidence of coronary artery disease. The question arises however, as to the relationship of the coronary artery disease to the Cushing's syndrome. Shall we assume that this patient independently developed coronary artery disease with coronary occlusion and later developed evidences of Cushing's syndrome due to carcinoma of the adrenal cortex? Certainly this is not an unreasonable assumption. Or, shall we assume that there is a more direct relationship between the Cushing's syndrome and the coronary artery disease and hypertension? Dr. Knowlton has already described the occasional occurrence of an adrenal cortical carcinoma existing for a prolonged period of time. It is remotely possible that the patient may have had a carcinoma of the adrenal cortex for a four or five year period that was characterized by hypertension but no other clinical evidence of Cushing's syndrome. This is possible but in my opinion, most unlikely.

I would assume, therefore, that this patient has had coronary artery disease and hypertension for a considerable period of time and subsequently coincidentally and entirely independently, developed an adrenal cortical carcinoma with all the manifestations of Cushing's syndrome.

Is there still another possibility and I would ask whether there were

any urinary catecholamine determinations? Is it possible that the patient had a pheochromocytoma and can we in any way associate the pheochromocytoma with her endocrine picture? This possibility is obviously a forced one. However, in a pheochromocytoma with a fixed hypertension and diabetes there may occur evidence of mild virilism and some manifestations which might conceivably be interpreted as those of Cushing's syndrome. But this would not be characterized by a very considerable increase in the urinary excretion of the neutral 17-ketosteroids or any significant elevation of plasma 17-hydroxycorticoids. We therefore come back to the central question as to whether we are dealing with two disease processes. Are we dealing with a woman who had hypertension and coronary artery disease who subsequently developed a carcinoma of the adrenal, or are we dealing with a patient who had carcinoma of the adrenal cortex from the very beginning which was responsible for the hypertension and only later produced the more obvious signs of a Cushing's syndrome? This latter hypothesis is difficult for me to accept and I would assume that the patient had hypertension and coronary artery disease and later independently developed a tumor of the adrenal cortex.

Now how did she die? The patient had recurrent episodes of heart failure and her death could be explained on the basis of sudden left sided heart failure. It is possible that she had a dissecting aneurysm, or perhaps a pulmonary embolus, but sudden death in patients with severe cardiovascular disease is not too unusual.

In conclusion, my impression would be that if she did not have, in addition to the adrenal cortical carcinoma, a pheochromocytoma, which would be extraordinarily rare, then I would say that this patient had independent hypertensive cardiovascular disease and that she subsequently developed a carcinoma of the adrenal cortex, with the production of the signs and symptoms of adrenal cortical hyperfunction.

DR. KNOWLTON: May we ask the question, did she have a chest x-ray on her first admission?

DR. KOTEEN: It was normal.

DR. KNOWLTON: Did she have glycosuria?

DR. KOTEEN: She did not. She had it on only one occasion.

DR. KNOWLTON: All of that would be in favor of her having antecedent coronary disease and subsequent development of the other situation which statistically, of course, would be far more likely.

CHAIRMAN KIDD: Except perhaps for one thing. In my own experience the incidence of myocardial infarction in 45 year old women is quite rare. I recall but a single case of death from acute occlusive coronary artery disease in a woman of this age in The New York Hospital in the last 12 years. That is a point against the feeling that we might be dealing here with two separate disease processes.

DR. KNOWLTON: Another point that interests me, Dr. Soffer, is the development of amenorrhea in this patient at age 41 which seems suggestive in relation to the point you raised. Would you care to comment further?

DR. SOFFER: We are confronted with a problem about which I am not clear in my own mind although I have thought a great deal about it. Her menopause had ostensibly begun at the age of 35. The last menstrual period occurred at age 41. We will accept 41 as the actual time of the menopause and she dies at the age of 52, eleven years later. Let us assume for a moment that she had only one disease process which therefore had been in existence for an eleven year period if we assume that the early menopause was an expression of adrenal cortical hyperfunction. We certainly cannot with all reason postulate that she had a carcinoma of the adrenal cortex for this period of time, particularly since carcinomas of the adrenal cortex are very malignant tumors. Therefore if we want to tie the two together we would have to assume that the tumor was originally a benign one, rather small in size and which subsequently became malignant. I am not prepared to engage in polemics as to whether a benign tumor does or does not become malignant as far as the adrenal cortex is concerned. In any event I would say that this is not acceptable to me at this time.

The question that Dr. Kidd has raised, of course, is a cogent one. The incidence of coronary thrombosis in women under the age of 55 is fortunately extraordinarily uncommon, except in the presence of hypertension, or in the presence of diabetes, and perhaps in the presence of hypercholesterolemia.

DR. FORKNER: Would you add one more thing to that, in the presence of amenorrhea?

DR. SOFFER: Yes. The early menopause is a significant point having to do in a sense perhaps with an early aging phenomenon. She had hypertension and angina the first time she was seen at The New York Hospital. We are not in a position to know how long she had hyper-

tension or whether it was present prior to the onset of the angina.

DR. KNOWLTON: Dr. Soffer, I would like to ask what your experience has been along the following lines: I have encountered two patients with Cushing's syndrome, who at operation were optimistically thought to have benign tumors—the tumors were encapsulated in each case. However, after remissions lasting a few months to two years, these patients suffered a recurrence of their Cushing's syndrome and at this time metastases gave proof of the malignant character of their tumors.

DR. SOFFER: It is a mistake to think that encapsulated adrenal tumors are necessarily benign. It might be of some interest to you, Dr. Knowlton, that of the 50 patients with Cushing's syndrome seen in our clinic over the past 15 years, half had an adrenal tumor and half were nontumorous. Of the half that had a tumor, approximately half were benign and half malignant. Of the malignant ones, perhaps a third were well encapsulated tumors. Occasionally one cannot be entirely sure, even histologically, as to whether an adrenal tumor is benign or malignant and you have to wait to see what happens. In any event, approximately a third of these carcinomata were well encapsulated tumors but histologically were classical carcinomata. Encapsulation, therefore, is no indication as to benignity or malignancy, and incidentally no indication at all as to the ultimate prognosis.

CHAIRMAN KIDD: I think this would be a very good time for us to gain a little further objective information about the clinical story. Dr. Poker, from the Department of Radiology of The New York Hospital, is here and we shall ask him now if he will be good enough to give us his interpretation of the chest films and also to show us the nephrotomograms.

DR. NATHAN POKER: (Slide) There is moderate cardiac enlargement. The prominence of the left ventricular contour has already been described as compatible with what we have seen. The pulmonary nodular density in the left lung field has also been described by Dr. Forkner and this also was compatible with what is seen in practice. Drainage is normally from an intrathoracic primary site. There are very few other situations that can cause pulmonary density. Among these we might mention multiple pulmonary filling defect, granuloma and fistula.

I should like to discuss the appearance of the lung field. It has been mentioned that a localized lesion is present at the right in the lung field. This is only true on this rather poor reproduction. On study of the

original film we saw diffuse accentuation of the pulmonary bronchovascular markings and interpreted this as pulmonary vascular congestion. We did not feel that a localized lesion was present in the right upper lung field.

(Slide) This is the nephrotomographic examination described in the protocol. Very briefly, nephrotomography is a procedure akin to angiocardiography in which a large amount of contrast agent is rapidly injected into the antecubital vein and shortly after that films of the abdomen are made at intervals designed to capture the contrast agent within the abdominal aorta, within the renal vessels, in the smaller branches of the renal vessels. Following the arteriographic phase, tomographic sections are made in the mid-caudal plane of the kidney so that we have a picture of the opacified renal parenchyma. By this method we can distinguish renal-space-occupying lesions, renal tumors, renal cysts and we can distinguish para-renal masses which displace or invade the kidney. Here we see the splenic artery, which has an unusually straight course and appears to be displaced in a cephalad direction. Usually, the splenic vein has a much more tortuous course than this. This is interpreted as compression of the splenic vein. We have the renal artery displaced downward and the outline of the opacified left kidney which appears at a somewhat lower level than normally. We see the upper pole of the left kidney which appears intact and because we do not see a contour abnormality in this area we felt this represented an extrarenal mass in the suprarenal area.

CHAIRMAN KIDD: *I have before me a number of questions some of which I am going to call upon Dr. Koteen to answer.*

One question is about the blood pressure reading of 165/150. This was, as I said earlier, a typographical error. The abstract should have read 165/115.

Another question is about a film of the skull; unfortunately this is not available.

Dr. Koteen, I shall ask you in succession three questions: Was there a gynecological examination for pseudohermaphrodism?

DR. KOTEEN: Yes. Dr. Soffer asked a question or implied a question which I should like to answer. I first saw this patient on November 7, 1950. I saw her three weeks later, when she had the second blood pressure reading. Following that I did not see her again until three and a half years later when she called me on the telephone with the story

of the pressure, chest pain.

DR. SOFFER: That answers an important question.

DR. KOTEEN: Although the implication is that she was under constant surveillance, we did not have the opportunity of seeing her during that three and a half year period. My notes describe the genitalia as entirely normal at the time of the acute myocardial infarction. I must confess that later examination did not include the genitalia. Later, when I became aware of the plethora, the greasy skin, etc., I did examine the genitalia and was much impressed by the marked hypertrophy of the clitoris in contrast to my previous examination in which I described the genitalia as normal.

CHAIRMAN KIDD: *May I ask you this question also, Dr. Koteen: Were pancreatic and liver function tests made? Did these disclose significant abnormalities?*

DR. KOTEEN: No. The only pancreatic study done was the glucose tolerance curve which, I believe, is described as elevated. No liver function studies were done. The cholesterol was 283.

CHAIRMAN KIDD: *Did you palpate any masses in the breast, the thyroid, or the ovaries?*

DR. KOTEEN: No, I did not.

CHAIRMAN KIDD: *Was there a blood uric acid determination?*

DR. KOTEEN: There was not.

CHAIRMAN KIDD: *I think I can take up the answers to the rest of these questions as I give the anatomical findings, but if there are any unwritten questions about the clinical aspects of the case or any divergent opinions that you would care to offer, this is the time to do it.*

DR. ANNA DANIELS: *What did the postmortem show?*

CHAIRMAN KIDD: I shall presently recite the postmortem findings. Are there other questions about the clinical findings? I may say that the anatomical findings here correlate, it seems to me, extraordinarily well with the clinical story. The only thing that takes away some of the pleasure that I usually have in disclosing them is the record that these three panelists have made in arriving at the diagnosis. But since I have reason to respect as well as admire them, I am going to forgive them their expertness this afternoon.

The first organ that I shall speak about is the heart, which showed a very definite thickening of the left ventricular myocardium. This we consider to be the result of the hypertension which was present

during some years preceding her death.

(Slide) I show you here the opened left ventricle. One can see that the myocardium is thickened. This increases the mass of the heart as a whole. It weighed 340 grams, which is just at the upper limit of normal and considerably above the normal for a woman of this age and body weight. The coronary arteries showed a focal atheromatosis which was widespread throughout those vessels. The anterior descending branch of the left coronary, about a centimeter from its ostium, was virtually occluded by an old fibrous atheromatous plaque, and this had brought about a scar which is rather indistinctly visible in the anterior wall of the left ventricle, and had led to a remarkable thinning of the wall in this area. All of this was obviously quite old, and we related it to the episode that she had had some years before her death. We did not find anywhere valvular changes or any evidence of fresh thrombosis, or occlusion, of coronary arteries nor any fresh infarction in the myocardium.

(Slide) The cause of death was a massive pulmonary embolism. One sees in these images a part of the femoral vein. In the vein is a thrombus which is perhaps 12 or 14 cm. long, loosely adherent to the vessel wall. This had given rise to a positive Homan's sign during the last two days of her life, and I could not include this fact in the protocol without giving away the anatomical diagnosis; this was the omission to which I referred earlier. Two thrombi were found loosely coiled in the pulmonary conus and obstructing both main pulmonary arteries. It seems obvious that these thrombi had reached the pulmonary conus and obstructed the arteries within a few moments before this woman's death.

(Slide) We found a tumor precisely where the radiologists and clinicians had suspected it to be—namely in the region of the left adrenal. Here we see the left kidney, and the tumor, which measured about 12x8x7 cm., viewed from the posterior aspect. One notes that the tumor is quite yellowish, and that it does infiltrate the upper pole of the left kidney; also that tumor can be seen growing within the adrenal vein, which leads into the inferior vena cava.

(Slide) This is the tumor after it had been dissected away from the bulk of the kidney and bisected. One sees on this cut surface that the fleshy parts of the growth are comprised of very yellowish tissue. In quite wide areas there has been necrosis of the neoplasm and hemor-

rhage into it. Yellowish tumor tissue extends into the adrenal vein and almost to the inferior vena cava but not into that vessel.

(Slide) This is a rather low power microscopic view of the malignant tumor, which we have classified as a carcinoma of the adrenal cortex. It is a rather highly vascular tumor. There are wide vessels filled with blood, and fibrous septa separate the tumor into lobules. The neoplastic cells are seen in tiny lobules.

(Slide) This is a much higher power microscopic view of a portion of the neoplasm and shows the cellular structure in greater detail. This slide—for which I am indebted to Dr. Nelson Holmquist, who made the postmortem examination and left a very lucid record of the case—shows the extreme pleomorphism and anaplasia of these neoplastic cells. They differ markedly one from another: many of them are binucleate; and the cytoplasm varies. For example, here is a tumor cell with the cytoplasm completely distended with clear vacuoles which I have reason to believe are fat. Any number of nuclear abnormalities are to be seen and the nucleoli are curiously enlarged so that they resemble nuclear inclusions. On the whole the cells resembled imperfect adrenal cortical cells.

(Slide) This is another section of the tumor showing one of the fibrous septa that break it up into lobules and the extraordinary vascularity of the growth—these being tumor cells and here a portion of the tumor which has become necrotic and in part calcified, as is shown by this purplish granular staining material. Here also one notes, in the necrotic portion of the tumor, elongated slits which have the character of cholesterol crystal slits as I shall show you perhaps somewhat better in another photograph.

(Slide) Here the elongated needle-like clefts left by the dissolution of cholesterol crystals during the process of embedding are plainly seen in a portion of the tumor that is not necrotic.

(Slide) Finally, this is an Oil Red O stain of a portion of the tumor to demonstrate the presence within the neoplastic cells of a great quantity of lipid which here stains orange red.

(Slide) This tumor, as I am sure you are by now aware, was malignant. It had metastasized quite extensively to the liver. Here one sees a number of tumor masses in the liver, some of them up to four or five cm. across, with normal hepatic parenchyma in between. This is a section of the lung and on both left and right sides one sees discrete

spherical metastatic nodules, some of them measuring up to 2 cm. across; these were distributed for the most part around the periphery of the lungs.

(Slide) There was also invasion of the upper pole of the left kidney. This was the extent of the spread of the tumor throughout the body. In addition there was a very pronounced generalized osteoporosis. I show you here a long segment of the vertebral bodies, mainly from the lumbar area. One can see how red the marrow is. I hope you will accept my testimony that the bony lamellae in the central portions of the vertebral bodies were exceedingly soft, so that one's finger sank into them on the slightest pressure. This slide shows the right adrenal which was atrophic, as Dr. Forkner predicted.

(Slide) Finally, there were changes in the pituitary. This was not abnormal on gross examination however, either in size or in shape. The organ weighed about 600 mg. which is about normal, and the sella was normal. Here is a slide of the pituitary, stained with Mallory's stain. The basophils display Crook's hyaline change in the cytoplasm. One sees that the basophils are generally devoid of basophilic granules and often contain vacuoles.

Our final anatomical diagnosis may be listed as follows:

1. Functioning carcinoma of the adrenal cortex with metastases in liver, lungs, and kidney:
   Hirsutism and frontal alopecia.
   Atrophy of the right adrenal.
   Generalized osteoporosis.
   Cooke's hyaline change of the basophilic cells of the pituitary.
2. Thromboembolism:
   Thrombosis of the left femoral vein.
   Massive fatal pulmonary embolism.
3. Hypertensive and arteriosclerotic cardiovascular disease:
   Hypertrophy of the heart.
   Old occlusion of the anterior descending branch of the left coronary artery.
   Myocardial scar in anterior wall of the left ventricle.
4. Multiple abscesses (hemolytic staphylococcic aureus) in skin and renal cortices.

We felt that the massive fatal pulmonary embolism was probably unrelated to the presence of neoplastic elements in the adrenal vein but was almost surely related to increased amount of thromboplastic substances circulating in the blood of this woman with a metastasizing carcinoma of the left adrenal, which had given rise to the metabolic changes that characterize Cushing's syndrome as our panelists have described.

If there are questions or comments, I shall be glad to have them now. Dr. Forkner, have you one?

DR. FORKNER: Will you tell us what the kidneys showed?

CHAIRMAN KIDD: I neglected to mention two anatomical findings. There was extensive furunculosis from which we cultured a hemolytic staphylococcus, and there was also an acute pyelonephritis, as you had predicted. This, however, was not extensive. There were merely a few cortical abscesses. The left kidney showed infiltration with tumor in its upper pole, but no significant changes otherwise.

DOCTOR: We agree that it is rare to have myocardial infarction in a woman under 50 years of age unless she also had atheromatosis. I don't know if her hypertension played any role whatever in regard to her myocardial infarction, or the atheromatosis. Would a tumor of this kind reduce the circulating cholesterol? We know it was within normal limits although not exceedingly low. Would that be a possibility?

CHAIRMAN KIDD: *Dr. Soffer, will you answer?*

DR. SOFFER: The exogenous administration of cortisone and cortisol (Compound F), is associated with the subsequent development of hypercholesterolemia. A patient with Cushing's syndrome almost always has an elevation of the serum cholesterol level. Whether 285 mg. per cent is elevated or not is in part dependent upon the normal standards of a particular laboratory. In our laboratory at The Mount Sinai Hospital, the normal values vary from 220 to 300 mg. per cent. In some laboratories the 285 mg. per cent might be somewhat elevated. In any event it would have to be considered the upper limit of normal, which is the kind of value that one often encounters in adrenal cortical hyperfunction with Cushing's syndrome.

DR. DANIELS: Did I understand correctly, that the thrombus came directly from the blood due to increased thromboplastin as the result of the neoplasia?

CHAIRMAN KIDD: It seems to me that the embolus probably broke away from the thrombus that was found in the left femoral vein on postmortem examination. In relation to the thrombus in the femoral vein, my point was that phlebothrombosis is exceedingly common in the terminal stages of neoplasia of many different sorts, not merely carcinomas of the adrenal cortex or pancreas and that this is unrelated to the presence of tumor cells within the blood vessels but probably has some relationship to thromboplastic substances which are liberated from the necrotic or proliferating neoplastic tissue throughout the body.

Dr. Forkner, can you elaborate on that point?

DR. FORKNER: I think that is true and perhaps the most common neoplasm with which thrombophlebitis is associated is carcinoma of the pancreas and then perhaps next in order are carcinomas of the liver and of the intestines.

CHAIRMAN KIDD: *Are there any other questions?*

DR. DANIELS: Why would you not call this a Cushing's disease in view of the tumor and the hypertension and all the other factors?

CHAIRMAN KIDD: *Dr. Knowlton, would you reply?*

DR. KNOWLTON: I think she had a form of Cushing's disease. She had in addition more of the andric elements than are commonly seen in Cushing's disease due to hyperplasia. This was probably due to the fact that the neoplastic tissue was producing not only those steroids normally secreted by the adrenal and secreted in large quantities by the hyperplastic gland, but also abnormal steroids, androgenic in nature, which led to the marked increase in her 17-ketosteroid excretion.

DOCTOR: She was maintained on anticoagulant therapy it is stated here. Nevertheless she developed femoral thrombosis in spite of th anticoagulants.

CHAIRMAN KIDD: *Dr. Koteen, can you reply to that?*

DR. KOTEEN: This patient was off anticoagulant therapy for many weeks.

SAME DOCTOR: That is different.

DR. KOTEEN: Once she developed the thrombophlebitis.

CHAIRMAN KIDD: *Dr. Koteen, have you other comments?*

DR. KOTEEN: We did two other studies on this patient which we might mention because they have diagnostic significance. They were not wilfully withheld however. The purpose, as described by the endocrinologists in giving the ACTH, was to see if we could stimulate

additional production of glucocorticoids in the blood stream, because of the hyperplasia we might anticipate elevation. We did the contrary test in giving the patient cortisone to see if we could suppress the glucocorticoids and we failed to do so. This is additional evidence of the tumor and at the same time we recorded the 17-ketosteroid excretions for eight days. Then we gave five days of cortisone to see if we could suppress the excretion of 17-ketosteroids and we again failed to do so. Perhaps Dr. Soffer would comment on that.

DR. SOFFER: May I ask a question first?

CHAIRMAN KIDD: *Certainly.*

DR. SOFFER: Could you tell us the origin of the cancer cells? Could you tell us where they come from, any one particular zone of the adrenal cortex?

CHAIRMAN KIDD: *No.*

DR. SOFFER: Could you say whether they originate in part from the reticular zone?

CHAIRMAN KIDD: *Oh, no! I think it would be mere speculation to say so in this case.*

DR. SOFFER: I am glad to hear you say that.

CHAIRMAN KIDD: *We feel we do well enough if we say they resemble cells of the adrenal cortex, not to undertake to differentiate them.*

DR. SOFFER: I admire your conservatism. I raise the question because it has been a point of contention concerning the relationship of the function of the reticular zone to the development of virilism. I might say that I am not yet convinced about this relationship.

I subjected this problem to a test one day. Our pathologist and I attempted to correlate this clinical picture of virilism with the location of the hyperplasia or tumor in one of the three zones of the adrenal cortex. We could never satisfactorily establish a consistent relationship. Concerning the point that Dr. Koteen raised in reference to the effect of cortisone on the pituitary elaboration of ACTH: This becomes important as a method of distinguishing between adrenal cortical tumor and hyperplasia as a cause of virilism. When one is confronted with the problem of a patient with the adrenogenital syndrome, as evidenced by virilism and characterized by a marked increase in urinary excretion of the neutral 17-ketosteroids, the first problem that arises concerns the possible presence of an adrenal cortical tumor or adrenal cortical hyperplasia. If a tumor is present the therapeutic approach is

obviously surgical. On the other hand, if the virilism is due to adrenal cortical hyperplasia more conservative medical measures are available.

The procedure introduced by Wilkins and his group is very helpful in distinguishing hyperplasia from tumor in patients with the adrenogenital syndrome. Adrenal cortical hyperplasia is ostensibly due to an increase in the pituitary elaboration of a fraction acting on the adrenal cortices and resulting in an increase in their size and increased secretion of androgenic material and reflected by an increased amount of neutral 17-ketosteroids in the urine. If cortisone or other glucogenic corticoid is administered to such patients this is followed by a decrease in urinary excretion of the neutral 17-ketosteroids. By contrast adrenal cortical tumors generally function autonomously, and with an occasional exception are independent of pituitary control. Under such circumstances, the administration of cortisone will not result in a decrease in the urinary excretion of the neutral 17-ketosteroids. Thus when a patient shows a considerable increase in the daily urinary excretion of the neutral 17-ketosteroids and the administration of cortisone over a five or six day period fails to result in a definite and marked decrease in the urinary excretion of these fractions this is good evidence in favor of the probable existence of an adrenal cortical tumor as the cause of the virilism.

CHAIRMAN KIDD: I note that our time is exhausted. I wish to thank Dr. Holmquist for making available to all of us his excellent postmortem record; Dr. Poker for the demonstration of his enlightening nephrotomograms; and the very distinguished members of this panel, Dr. Forkner, Dr. Knowlton and Dr. Soffer for their brilliant and precise clinical discussions. I declare our meeting adjourned.

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April 17—PROBLEMS OF SCHIZOPHRENIA IN CHILDHOOD (panel): Section II

April 24—NEWER CONCEPTS IN DIET THERAPY—Herbert Pollack, *Associate Professor of Clinical Medicine, New York University Postgraduate School of Medicine, New York City.*

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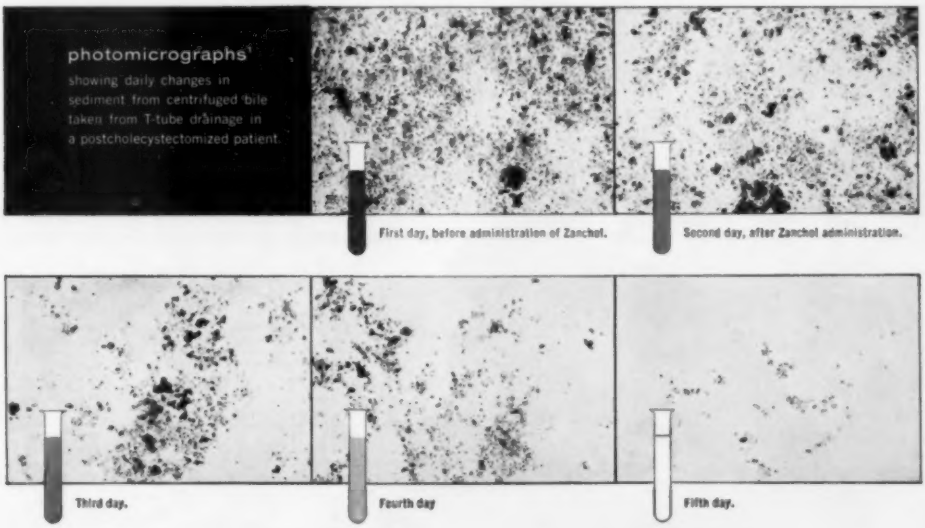
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1. McGowan, J. M.: Clinical Significance of Changes in Common Duct Bile Resulting from a New Synthetic Choleretic, Surg., Gynec. & Obst. *103*:163 (Aug.) 1956.

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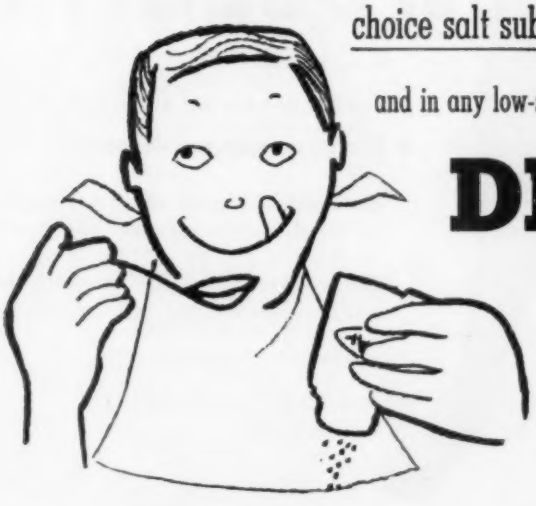

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metaphosphate produced markedly higher blood levels than capsules containing either the corresponding base or the hydrochloride alone. In addition, the average levels derived from the tetracycline base or the chlortetracycline base were higher than those produced by the corresponding hydrochloride though lower than those resulting from the mixture containing the base and sodium metaphosphate. In the study with chlortetracycline[6] capsules containing a mixture of the hydrochloride and sodium metaphosphate were also included in the crossover, and the average levels produced by these capsules were the same as with the mixture of chlortetracycline base with sodium metaphosphate.

Although the enhancement of blood levels of tetracycline by phosphate, either complexed to the tetracycline or mixed with the base or the hydrochloride, thus seemed fairly well established, some doubts still remained because certain reliable observers (including many whose results have not been published) failed to confirm the findings with the materials and methods they used. Further confusion seemed to be added by a subsequent report of Welch et al.,[7] who, in repeating a crossover study with capsules of tetracycline phosphate complex and tetracycline hydrochloride with and without sodium metaphosphate, found much hig

"...Tetracycline hydrochloride and citric acid, in an encapsulated mixture, produced higher serum concentrations and greater urinary excretions, and hence better absorption of tetracyclines, than any other preparation studied..."

cycline base. Dicalcium phosphate and food resulted in lower, and sodium metaphosphate in higher, serum antibacterial activity than was observed in their absence. Oil and sorbitol did not interfere with tetracycline absorption.

Dicalcium phosphate is widely used as a filler in various capsules, including those of the tetracyclines. The authors cite a large number of other studies that implicate the presence of calcium ions as the cause of the reduced absorption of tetracyclines and show that citric acid can partially neutralize this effect. The depressing effect of food on the serum levels of tetracycline is likewise explained by the goodly amount of minerals contained in commercial laboratory diets, and they postulate that the multivalent cations may be responsible for the poorer absorption of the drug. The authors could not explain the failure of citric acid to enhance serum concentrations when administered with tetracycline base in contrast to its marked effect when given as the hydrochloride. However, they hypothesized that the ability of citric acid to enhance serum levels of tetra[illegible] to its ability to form comple[illegible] unavailable for [illegible]

[illegible] last mentioned paper of [illegible] et al.[8] indicates that in their study the capsules [illegible] tetracycline hydrochloride, chlortetracycline hydrochloride and tetracycline phosphate complex all contained dicalcium phosphate as a filler, whereas the capsules containing citric acid and sodium hexametaphosphate did not contain any dicalcium phosphate. This could clearly explain the discrepancies noted in that study. Likewise, the inconsistencies in other studies may very well have been due to the presence of calcium as fillers in some of the capsules and not in others.

This, however, fails to explain the most recent findings of Welch and Wright,[10] who compared the absorption of three capsules, each containing 250 mg. of oxytetracycline hydrochloride — one without any adjuvant, one with 250 mg. of citric acid and the third with 380 mg. of sodium hexametaphosphate; no other filler was contained in any of these capsules. In triple

of [illegible] were published simultaneously with the last mentioned report of Welch et al.[7] These data were based on thoroughly controlled studies both in rats[9] and in man[6] and include additional findings that serve to explain, fairly conclusively, the various discrepancies that have been mentioned.

The experiments in rats[9] were carried out to study the effects of citric acid, dicalcium phosphate, sodium metaphosphate, food, oil and sorbitol on the serum antibacterial activity produced by the administration of tetracycline hydrochloride or tetracycline base. Citric acid administered in equal weight with tetracycline hydrochloride gave the highest concentrations of all the preparations studied. No enhancing effect was obtained from citric acid when given with tetra-

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Tobacco and Health,
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Editorial.
The New England Journal of Medicine.
258:97-99, (January 9) 1958.

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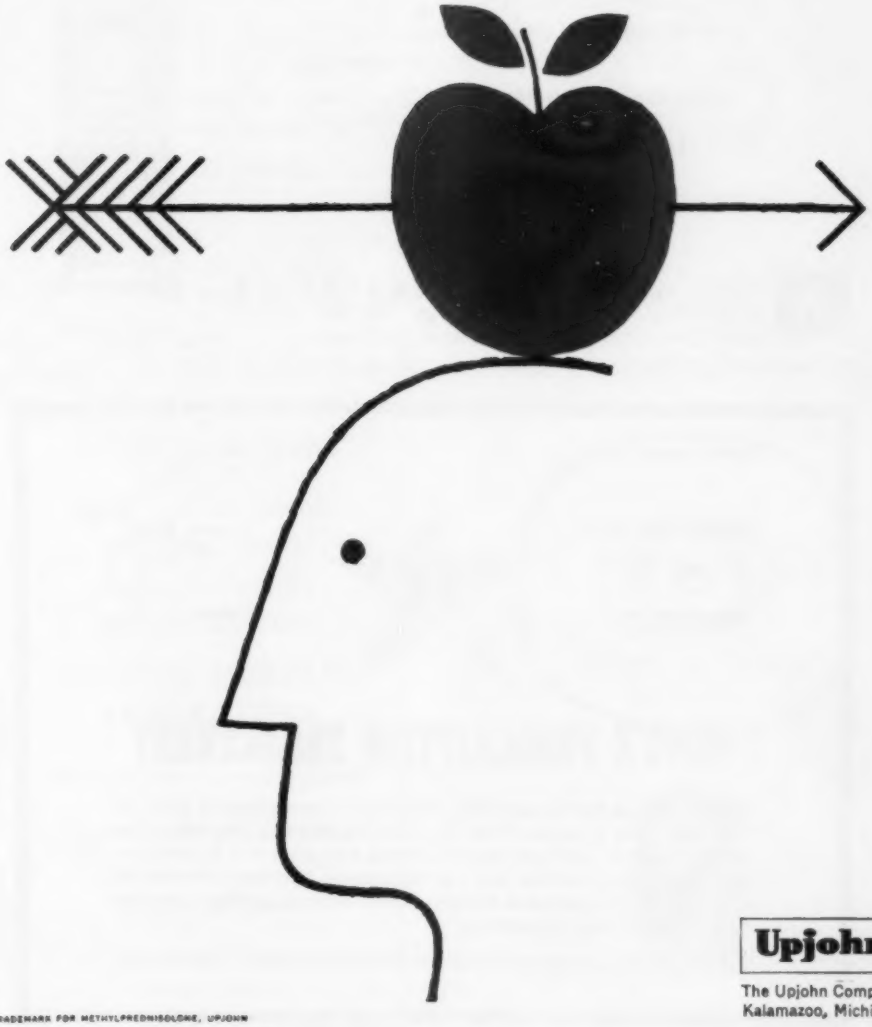

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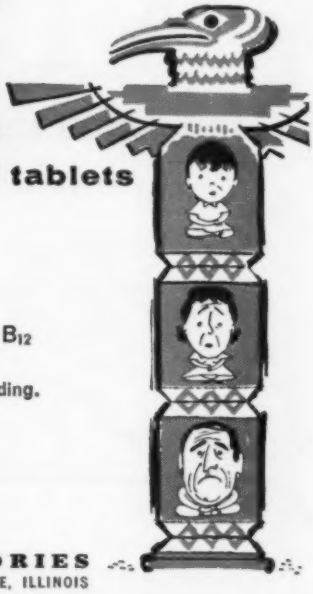

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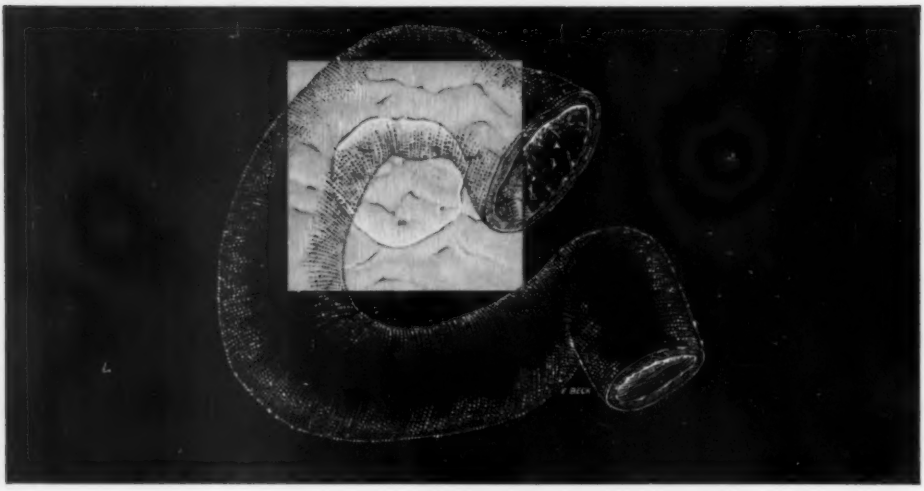

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*Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. **160**:1221, 1956.

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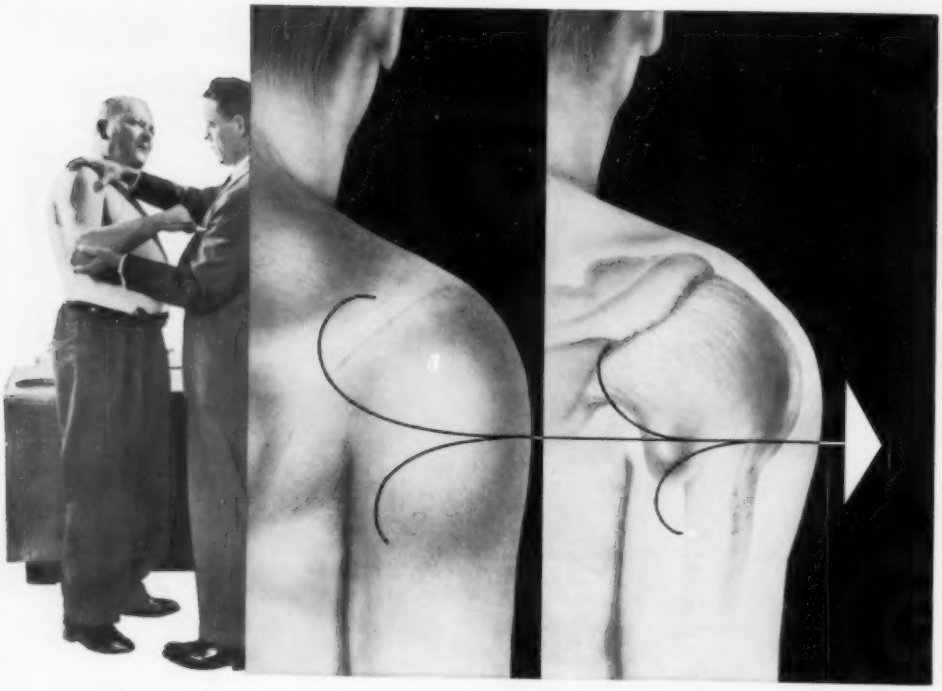

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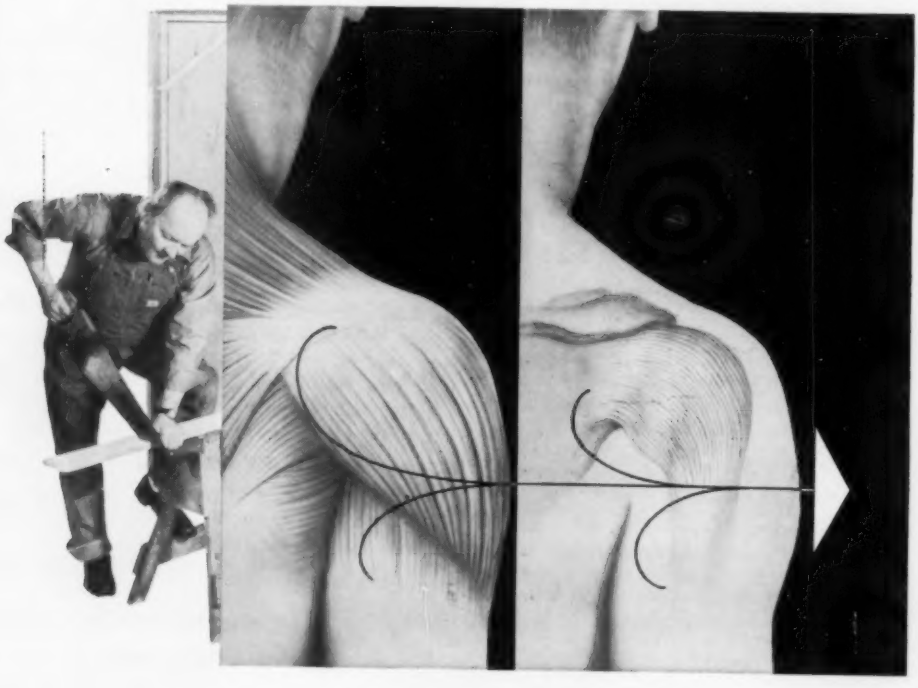

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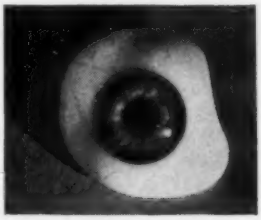

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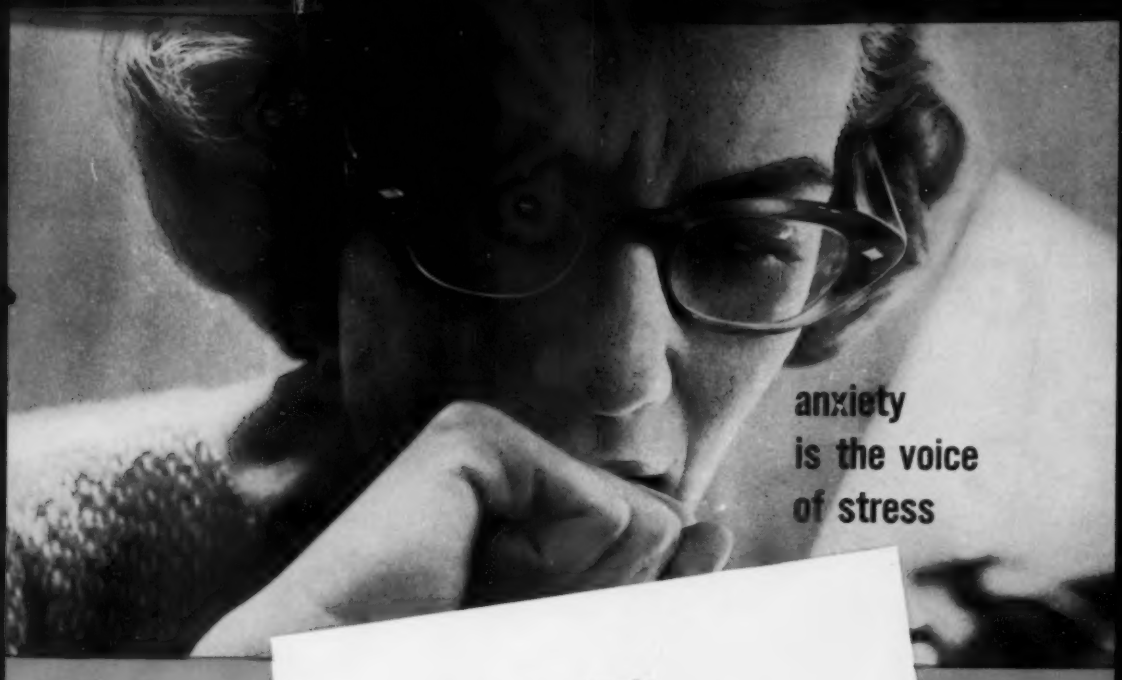

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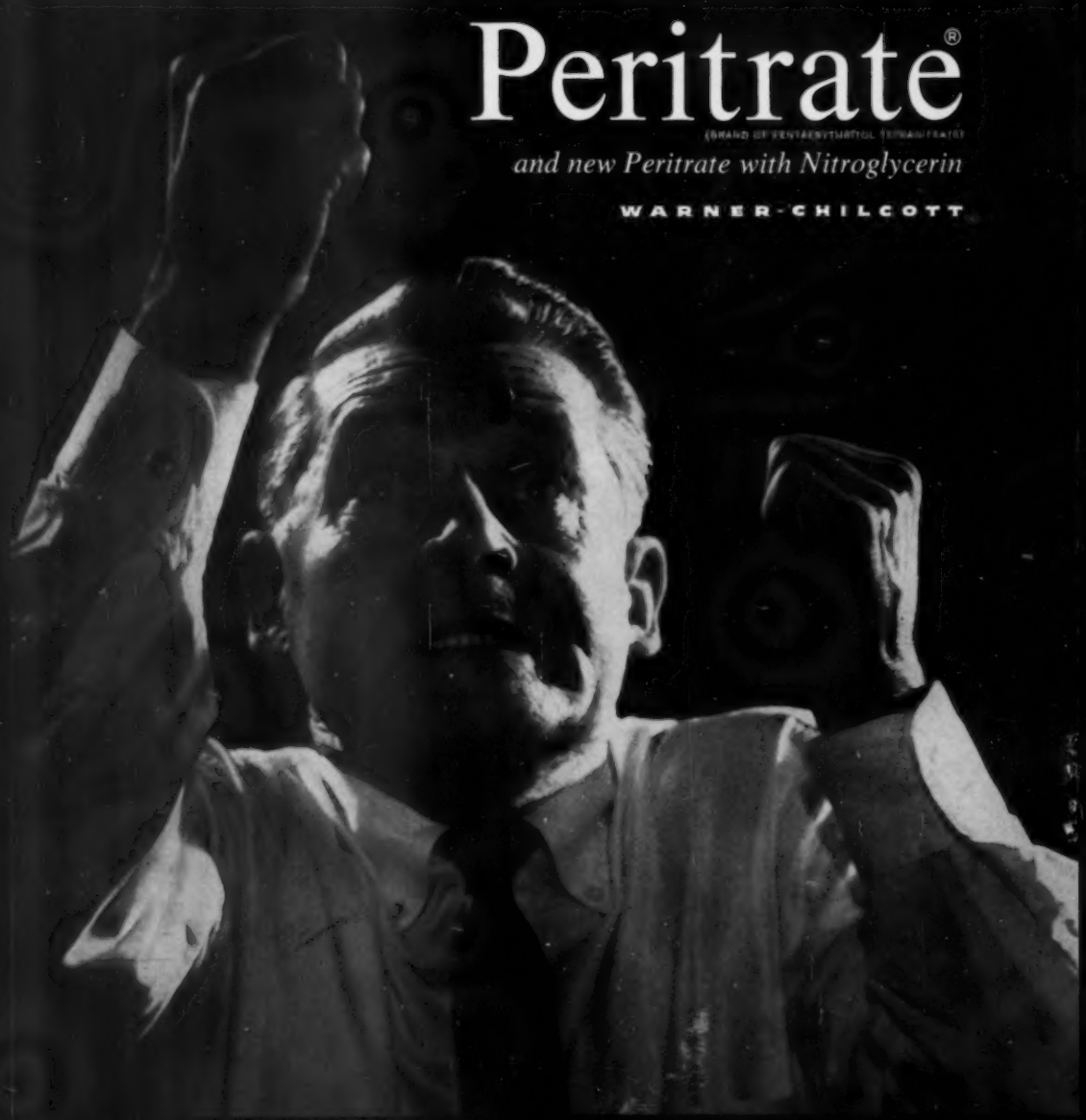

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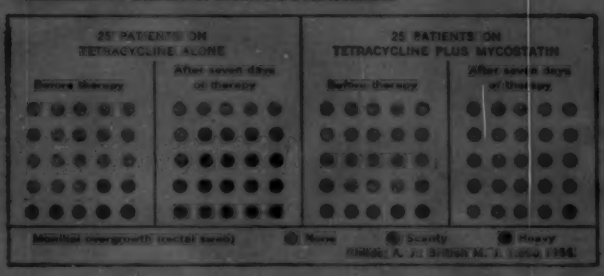

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